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OBSERVATIONS ON THE NATURE OF THE BENCE JONES ALBUMIN.

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The clinical history of the patient, whose urine I was enabled to study through the courtesy of the attending physician, Dr. N. E. B. Iglehart, of Baltimore, will be reported in greater detail at another place by Dr. L. P. Hamburger. A preliminary report has appeared in the *Johns Hopkins Hospital Bulletin*[1] of February, 1901. From this I have extracted the following brief account of the patient's illness, which is supplemented by a communication from Dr. Iglehart on the subsequent course of the disease.

The patient, a lady, aged forty-nine years, whose previous health had been good, was suddenly seized with sharp pain over the ninth left rib near its cartilaginous attachment (August, 1900). The pain was severe, and increased on deep inspiration. There was tenderness on pressure over the painful point. The condition at the time so nearly resembled a fracture that it was supposed the patient had injured the rib. A history of trauma, however, could not be obtained, and there was neither crepitus nor a friction rub. Within three weeks the pain had disappeared. She was again seen in September, and at that time complained of nausea, without apparent cause. She had lost thirteen pounds in weight, and her general health had manifestly suffered. Early in October she was again seized with pain, but this time in the region of the eighth rib, in the mid-axillary line. The patient then remarked that since the past summer she had taken more water and had voided a larger quantity of urine than usual (on one occasion 3500 c.c. were passed in twenty-four hours).

[1] L. P. Hamburger. Two Examples of Bence Jones Albumosuria Associated with Multiple Myeloma.

Dr. Osler saw the patient on November 30th, when, aside from a slight pallor of the visible mucous membranes, the physical examination was negative. In February of the following year a slight but definite elevation was palpable over the eighth right rib in front, of the size of a lima bean. The points referred to continued to be tender to pressure throughout the life of the patient. Subsequently she suffered a great deal of pain, the attacks becoming more and more frequent, but separated even then by periods of comparative comfort. Especially in the upper part of the left thigh there was much pain, which began about three months before death. For a while she used a cane; later she was obliged to resort to crutches, and finally she could not walk at all, and had to take to a wheel-chair. There was no deformity of the bone apparent, and palpation revealed no thickening of the femur, but it was very painful. There was marked muscular atrophy. The general loss of flesh increased, and toward the end amounted to about forty pounds. Nausea and vomiting became more and more marked, and were finally uncontrollable. Even small amounts of water could not be retained. The anæmia also increased markedly, but at no time suggested a pernicious type, so far as the general appearance of the patient went. An examination of the blood, however, was not made. The polyuria which was observed earlier in the disease continued to the last three weeks, but was not so marked as at first. During the last ten days the urine was scant, but the amount had not been estimated. Five days before death spontaneous fracture of the left femur occurred in its upper third, and with gradually increasing weakness death occurred on August 16, 1901. A complete autopsy, unfortunately, could not be made. Examination of the sternal end of what was regarded as the eighth right rib, however, very curiously, showed no abnormality.

The diagnosis of multiple myeloma was made at the time of the second attack of pain, on the basis of a urinary examination. Of this Dr. Hamburger writes as follows: "A specimen taken from the collected amount of twenty-four hours (3500 c.c.) was very pale, of acid reaction, with a specific gravity of 1004. It gives a white ring when floated over nitric acid. Heated to a temperature of about 55° C. a heavy, milky-white precipitate appeared. On boiling the fluid becomes clearer to become more turbid again on cooling. The addition of acetic acid to the fluid after reaching its maximum turbidity causes it to clear again. A few drops of nitric acid yield a precipitate which dissolves completely on boiling and reappears on cooling. In the Esbach albuminimeter the proteid content reached 0.27 per cent. The urine gives a strong biuret reaction. No casts were seen in a centrifugalized specimen. From these reactions Dr. Hamburger concluded that the urine contained the so-called albumose of Bence Jones, which, according to Kahler, is only found in cases of myeloma. This diagnosis was accordingly made. With Dr. Hamburger's consent I then undertook a more detailed study of the substance in question, with which the present paper has to deal. Through the courtesy of Dr. Iglehart about 16,000 c.c. of the urine were placed at my disposal, which was partly examined at once, partly after preservation with thymol or chloroform.

The urine was sent to me in bulk, without any attempt at separate collection, for periods of twenty-four hours, so that I am unable to give accurate figures in this respect from personal knowledge. Dr. Iglehart, however, informs me that during the period of polyuria, which was first

noted about August 10, 1900, and which extended over nearly a year, the average elimination varied between 2000 and 3500 c.c.

General Properties of the Urine. The urine was very pale and markedly cloudy. Microscopical examination showed that the turbidity was referable to numerous epithelial cells, derived from the genitals, and a fairly large number of leucocytes, probably of the same origin. There were no crystalline elements, no red blood-corpuscles, and no casts. Even after standing for five months a crystalline deposit of the albuminous body was not observed, nor did the substance separate out in amorphous form.

As in Magnus-Levy's case, it was noted that the urine underwent ammoniacal decomposition much less readily than is common. The reaction was constantly acid; the specific gravity usually low, never exceeding 1015.

A study of the common constituents of the urine was not made, but it was noted that uric acid and indican were not increased and that sugar was absent. Special attention was directed to the behavior of the peculiar albuminous body, which was present in considerable amount. Quantitative estimation (gravimetrically) on two occasions gave 0.5072 and 0.5124 per cent. These higher figures, however, were only found in the first lots of urine, while later on the amount was much smaller, and an examination of a 5-litre specimen which had been kept over the summer showed the presence of only about 0.025 per cent.

The general reactions which were obtained with the native urine are the following:

1. Upon the application of heat the acid urine remains clear until a temperature of about 52° C. is reached, when the liquid begins to show a milky turbidity. This rapidly increases in intensity, and at 55° C. the entire volume of urine is perfectly opaque, so that the bulb of the thermometer can no longer be seen in the test-tube. When heated still higher the milky turbidity is replaced by the appearance of flocculi, but even as the boiling-point is reached the urine can scarcely be said to have become clearer. On subsequent cooling the flocculent precipitate is seen at the bottom of the tube as a peculiar, granular-looking sediment, and its amount does not suggest an increased precipitation during cooling.

2. Upon the addition of a drop or two of a 25 per cent. solution of nitric acid to a few c.c. of urine a slight cloud forms, which disappears on shaking. When more of the acid is added an abundant precipitate results, which is insoluble in a large excess of acid (ten times the original volume). On heating the acid solution the albuminous substance first coagulates to a dense mass, but dissolves almost entirely on prolonged boiling, with the formation of a pink foam. On subsequent cooling the precipitate reappears, to disappear again (almost entirely) on boiling.

It is noteworthy that *with the cold nitric acid test, applied in a conical glass, a far more abundant precipitation is manifestly obtained than upon the application of heat.*

3. With hydrochloric acid and sulphuric acid similar results are obtained. As a rule, three drops of the concentrated acid (as also of nitric acid) were necessary to bring about a precipitation of the albumin, which did not disappear on shaking.

4. Carbonic acid was without effect, even if the urine had been copiously diluted.

5. Upon the addition of acetic acid, even in large excess, no precipitate results. On subsequent heating the liquid remains clear.

6. Phosphoric acid also does not cause a precipitation of the substance.

7. The addition of picric acid (13 to 14 drops of a saturated solution for 5 c.c. of urine) causes the formation of a flocculent precipitate, which increases in amount on heating, but does not disappear entirely on boiling. With the mineral acids complete clearing was not always observed, but in this case the urine remained much more turbid.

8. Tannic acid causes complete precipitation after the previous addition of acetic acid. The precipitate disappears to a great extent on boiling.

9. With phosphotungstic acid, in the presence of hydrochloric acid a heavy precipitate results, which does not disappear on boiling.

10. With potassium ferrocyanide and acetic acid a precipitate is obtained which is but little soluble at 100° C.; it increases on subsequent cooling.

11. On neutralization with a dilute solution of sodium hydrate or ammonia no precipitation results.

12. On acidifying the urine with acetic acid and subsequent neutralization with sodium hydrate a precipitate results, which dissolves practically entirely on boiling and reappears on cooling.

If an excess of sodium hydrate is added to the neutral solution the neutralization precipitate disappears, and it is noteworthy that no precipitate now appears on heating; but if then the solution is again neutralized with acetic acid a neutralization precipitate appears; but, in contradistinction to the first, this does not disappear on boiling, and is only slightly soluble in the presence of a large excess of the acid.

13. If the urine is first rendered alkaline with sodium hydrate and is then neutralized with acetic acid, a neutralization precipitate results, which, as in the last instance, does not disappear on boiling, and is only slightly soluble in a large excess of the acid.

In order to obtain such neutralization precipitates, however, not too little acid or alkali must be added, as otherwise no precipitate occurs on subsequent neutralization. In one instance I treated 20 c.c. of a solution of the isolated substance (precipitation with ammonium sulphate and dialysis for eight weeks) with a few drops of hydrochloric acid—such that the solution contained 0.36 per cent. On neutralization with sodium hydrate a precipitate was then not obtained, even on heating; but this developed at once on acidifying the hot solution with acetic acid.

14. Similar results as in 11 and 12 were obtained with dilute mineral acids.

15. Alcohol, when added in the proportion of two volumes for one of the urine, causes complete precipitation of the substance; and it is to be noted that after prolonged contact the albumin loses its subsequent solubility in water.

16. On treating the urine with an excess of a saturated solution of common salt (two to three times the original volume) no change occurs, but on heating the substance is precipitated, and on subsequent boiling the solution remains turbid.

17. Upon the addition of a saturated solution of common salt to the acidified urine (acetic acid) complete precipitation occurs, which is hastened by heating to about 50° C. On boiling there was no evidence of clearing.

18. Saturation of the urine with rock salt at ordinary temperatures causes a partial precipitation, which is soluble in water. Saturation at from 35° C. to 40° C., on the other hand, results in the complete precipitation of the albumin, and it is noteworthy that this precipitate is insoluble in water.

19. Upon the addition of two and one-half volume of a saturated solution of magnesium sulphate to the urine no change occurs, even after the addition of acetic acid; but on saturating the acidified solution with the salt in substance the albumin is precipitated. This occurs at once if the urine is first saturated with the salt, and acetic acid is then added. *Saturation of the urine with magnesium sulphate without the addition of acetic acid caused no change. In a dialyzed specimen, however, which presented a neutral reaction complete precipitation could be produced by saturation with the salt in question.* (See below.)

20. Saturation of the acidified urine with sodium sulphate in substance causes the precipitation of the albumin, as in the case of magnesium sulphate. The addition of an equal volume of a saturated solution of the salt causes partial precipitation.

21. A saturated solution of ammonium sulphate, when added in the proportion of two volumes for one volume of urine, causes the complete precipitation of the substance, the reaction being neutral.

22. On dialysis the substance is not precipitated, nor does it pass through the membrane.

23. Millon's reaction: On heating the flocculent precipitate turns red.

24. Biuret reaction: An intense purplish-violet is obtained if a sufficient amount of the copper solution is added; if but little is present the color is red.

25. Reaction of Adamkiewicz: A beautiful purplish-violet results.

26. Hydrochloric acid reaction: A reddish-violet color results, but is not nearly so intense as with Adamkiewicz's test.

27. The sulphur test yields a positive result (brown color on boiling).

28. The xanthroproteic reaction is positive.

29. Molisch's reaction is not well marked, but occurs on prolonged standing.

Reactions of the Isolated Substance.[1] To isolate the Bence Jones substance the urine was neutralized and precipitated with twice its volume of a saturated solution of ammonium sulphate. The copious precipitate was filtered off with the aid of a suction pump, and kept as such in a two-thirds saturated solution of the salt. When first precipitated it appeared white; but later, after exposure to the air, it assumed a pinkish tint, which subsequently changed to a light terra-cotta.

To purify the substance the material was repeatedly dissolved in hot water, reprecipitated with ammonium sulphate, and finally dialyzed. It was noted, however, that it was impossible to remove all the sulphate

[1] Through the kindness of Dr. Edward S. Wood, of Harvard, I was enabled to compare the reactions of my isolated substance with a product which he obtained from the urine of a patient of Dr. Fitz (Case 13, see below). The corresponding report follows below.

in this manner, even after exposure to running water for nearly three months. The resulting solution was used for the common tests, while it was found necessary to resort to some other method of purifying the substance in order to obtain material that could be employed for purposes of elementary analysis. To this end the filtered urine was slowly heated and the albumin thus coagulated. The coagulum was washed with water, dissolved by the aid of a little sodium carbonate in boiling water, and repeatedly precipitated with alcohol. The precipitated substance was finally placed in the dialyzer for twenty-four hours and the contents of the dialyzer treated with double their volume of alcohol, so as to recover a portion of the substance that had passed into solution. The material was washed with absolute alcohol and ether, pressed out between filter paper, and dried at 105° C., when it changed to a horny, brittle mass. Purified in this manner the substance was practically free from ash, while the crude material apparently contained both iron and phosphorus. Two nitrogen estimations gave 15.12 and 15.26 per cent.

The dried substance is almost insoluble in water and dilute saline solutions at ordinary temperatures, and dissolves with difficulty even in hot water unless a trace of sodium carbonate is added. In that event, however, solution takes place with comparative readiness on heating, and it is to be noted that the solution remains clear on subsequent neutralization, providing that a sufficient amount of water is present and that too much of the soda has not been added. The *moist* substance, on the other hand, is soluble even in cold distilled water, though not so readily as the references in the literature would lead one to think. It is noteworthy that it is not nearly so easily soluble as the common water-soluble digestive albumoses. On prolonged contact with alcohol the material is rendered insoluble in water and dilute saline solutions; in such an event, however, as has already been pointed out, solution in water can be effected on heating after the addition of a little soda or a few drops of hydrochloric acid. Such a precipitate, moreover, is soluble in dilute ammonia.

The solution of my isolated substance (obtained, as first described, by precipitation with ammonium sulphate and subsequent dialysis) was of neutral reaction, and on heating became but slightly turbid. If a small amount of salt and a drop of acetic acid were added, however, coagulation occurred as in the case of the native urine. Heated *slowly*, immersed in a beaker with water, the first trace of turbidity was noticeable at 54.5° C.; at 55° C. the entire bulk of the solution was cloudy; at 55.5° C. it was decidedly opaque; the maximum intensity was reached between 58° C. and 60° C. At about 70° C. the general opacity was replaced by the appearance of a flocculent precipitate, which gradually assumed a more granular appearance and finally settled to the bottom in the form of microscopical spheroliths, while the supernatant fluid became clear. An actual solution of the substance was not observed.

On heating the solution and then adding concentrated nitric acid a flocculent precipitate occurred with the simultaneous appearance of the xanthoproteic reaction.

Upon the addition of nitric acid to the cold solution a precipitate occurred, which, in contradistinction to the native urine, was but little

soluble on the subsequent application of heat, even at 100° C., and on cooling no appreciable increase in turbidity was noted. The same result was obtained with potassium ferrocyanide and acetic acid.

On treating the solution with an acid or an alkali and subsequent neutralization a precipitate occurred, which was soluble in an excess of the reagent. To obtain this precipitate, however, it was necessary to add a definite amount of acid or alkali; if too little was used no precipitate occurred. This is shown by the following example: 20 c.c. of the clear neutral solution were treated with an amount of hydrochloric acid such that the solution contained 0.36 per cent. On neutralization with sodium hydrate no precipitate occurred, and on boiling the solution remained clear. If, then, a little acetic acid was added, however, while the solution was still hot, precipitation occurred at once.

On saturating the *neutral* solution with magnesium sulphate at the temperature of the room, complete precipitation occurred on standing for less than twenty-four hours.

The limits of precipitation with ammonium sulphate were 2.3 and 3.8, respectively.

On salting with common salt to saturation a partial precipitation of the substance occurred at ordinary temperatures, the reaction being neutral. On adding two to three times the volume of a saturated solution of common salt to a solution of the isolated substance, however, no precipitation occurred so long as the reaction was neutral, but on adding a few drops of acetic acid a turbidity occurred at once.

On salting with rock salt at ordinary temperatures an abundant precipitate also occurred, which, like the one preceding, was soluble in water.

Upon the addition of a dilute solution of copper sulphate precipitation occurred at once. The biuret reaction was positive—an intense purplish-violet.

In its other reactions the isolated substance showed the same general behavior as the native urine (which see).

From these reactions of the urine and the isolated substance it is clear that the albuminous body in question is not one of the common albumins which we meet with in ordinary cases of albuminuria, but clearly resembles the substance which was first observed by Bence Jones and MacIntyre in a case of supposed osteomalacia.

Special Reactions. Behavior of the Substance on the Application of Heat. Of especial interest is the behavior of the urine on the application of heat. Quite constantly the first indication of a turbidity appeared as the 52° C. mark had just been passed and before 53° C. had been reached. At 55° C. the liquid had become quite opaque, so that it was impossible to see the markings of the thermometer where it was immersed, and still later even obscuring the bulb of the instrument. The turbidity was distinctly milky in appearance, and was first noted in the surface layer, from which it gradually extended downward. Later the starting-point of the precipitation appeared to be wherever the urine came in contact with the walls of the test-tube or the bulb of the thermometer. Heated beyond 55° C., viz., to 60° C., the turbidity sometimes increased a little more, providing that the elevation of the temperature was brought about gradually, as by immersing the tube in a large beaker full of water and heating this with a comparatively small flame. On further heating no increase in opacity was noted, but

as 75° C. to 80° C. was reached the milky turbidity gave way to the appearance of a coarsely flocculent precipitate, which, however, did not dissolve even at 100° C. If left to itself the precipitate settles to the bottom, while the supernatant fluid becomes clear, and remains clear on gradual cooling. If, however, the liquid is suddenly cooled, as by immersion in cold water, the supernatant fluid becomes turbid. A similar result is reached on filtering the hot liquid, when the first portion which passes through at once turns cloudy on coming in contact with the cold walls of the tube or beaker.

Providing that the process of heating is carried on very gradually and the urine is then allowed to cool of itself, a solution is obtained on filtration which no longer becomes turbid on subsequent heating at any temperature, but in which an albuminous substance is manifestly still present. Barring its different behavior toward heat, this solution gives the same general reactions as the native urine, viz.:

1. On treating with potassium ferrocyanide and acetic acid the solution becomes turbid, and on heating the turbidity does not disappear, but becomes even more pronounced. At 100° C. it is but slightly soluble.
2. With nitric acid a marked reaction is obtained.
3. After the addition of acetic acid, even in excess, the solution remains clear.
4. A marked biuret reaction is obtained—a purplish-violet, as in the native urine.
5. Treated with an equal volume of a saturated solution of common salt, no change occurs; but upon the addition of a few drops of acetic acid a turbidity results, which increases upon the application of moderate heat, but disappears on boiling, to reappear on cooling, etc.
6. Treated with two volumes of a saturated solution of ammonium sulphate the albuminous substance is completely precipitated.

The peculiar behavior of the urine on heating, on first consideration, suggested the presence of two distinct albuminous bodies in the urine, one of which could be coagulated by heat, while the other was apparently non-coagulable. It was ascertained, however, that such was not the case, and that it is possible by a suitable variation of the reaction, and by increasing or diminishing the amount of salt present, to increase or to diminish at will the relative amount of the coagulable as compared with the apparently non-coagulable portion. With an alkaline specimen it was thus found that after heating a much larger amount of the albumin remained in the filtrate than in the case of the acid urine, and as I have already indicated it is possible to completely precipitate the total amount of the substance by heating, after the previous addition of an equal volume of a saturated solution of sodium chloride to the acidified urine (acetic acid). In such an event the resulting filtrate is free from albumin.

It was also noted that the rapidity of heating is of marked influence upon the extent to which coagulation occurs. The more gradually this is done the more extensive is the coagulation. That the temperature at which this occurs is also dependent, to a certain extent at least, upon the amount of salt present was first shown by Magnus-Levy, and was also noted in the present instance. It was thus ascertained that whereas coagulation occurred in the native urine at a temperature of from 52.5° C. to 54° C., it was necessary to heat to 55° C. or 56° C. if a double volume

of a saturated solution of sodium chloride had been added. The further addition of salt then lowers the temperature of coagulation, and on saturating the urine with salt in substance complete coagulation may occur at 37° C. already if the liquid is kept at this temperature for several hours.

This influence of the relative amount of salt upon the degree of heat at which coagulation occurs is well shown in the following table, which is taken from Magnus-Levy:

Urine.	*20 per ct. salt sol.*	*Water.*	*First turbidity at*
2 c.c.	0.0 c.c.	2.0 c.c.	54.0°
2 "	0.2 "	1.8 "	54.5
2 "	0.4 "	1.6 "	55.0
2 "	0.8 "	1.2 "	55.0
2 "	1.2 "	0.8 "	55.5
2 "	1.6 "	0.4 "	56.0
1 "	3.0 "	0.0 "	56.5

Ammonium chloride, in my experience, did not influence the temperature of coagulation, while it apparently renders the precipitated substance more readily soluble at 100° C. This, however, is only observed if a definite amount of the salt is present, which should not exceed 1 to 2 per cent. saturation. At times, moreover, no result at all was obtained without any apparent reason. On one occasion two specimens of urine were diluted, the one with 2 c.c. of a saturated solution of ammonium chloride and the other with water. On heating neither became especially cloudy (the heat was rapidly applied). On cooling the slight turbidity persisted and even increased to a slight extent. On subsequent heating the ammonium chloride specimen now became more turbid than the control, and did not clear whatever on boiling. Upon the addition of a little acetic acid the turbidity increased even more.

Of great interest in this connection is the observation of Spiro[1] that the addition of urea to solutions of albumins increases the degree of temperature at which coagulation occurs, and that a point may be reached at which no coagulation whatever takes place. In accordance with Hofmeister's suggestion, that this might possibly account for the varying statements as regards the solubility of the precipitated albumin of Bence Jones at 100° C., Magnus-Levy undertook a special examination of his substance in this direction. His results are quite in accord with those reached by Spiro in the case of egg albumin and serum albumin. I have repeated this work, and was able to show that, as a matter of fact, a point is reached, on the gradual addition of a urea solution in increasing amounts, at which coagulation no longer occurs; but I was not able to demonstrate that the temperature of coagulation was correspondingly raised. So long as a turbidity occurred at all the temperature was the same until a certain percentage was reached, when the solution remained clear altogether. These results are shown in the following tables:

[1] K. Spiro. Ueber die Beeinflussung der Eiweisscoagulation durch stickstoffhaltige Substanzen, Zeit. f. physiol Chem., 1900, vol. xxx. p. 182. See also the recent work of W. Pauli and P. Rona, Untersuchungen über physikalische Zustandsänderungen d. Kolloide, Beiträge z. chem. Phys. u. Pathol., 1902, vol. ii. p. 1.

EFFECT OF UREA UPON THE COAGULATION OF BENCE JONES ALBUMIN

Urine (neutral).	Urea solution (50 per ct.).	Water.	Per cent. of urea added.	On warming.	At 100° C.	On cooling.	Repeated warming and cooling.
2 c.c.	0.0 c.c.	2.0 c.c.	.....	Marked turbidity.	Slight clearing.	Slight increase.	The same.
2 "	0.2 "	1.8 "	2.5 per ct.	Marked turbidity.	Marked clearing.	About the same.	The same.
2 "	0.4 "	1.6 "	5.0 "	Momentary cloud.	Clear.	Clear.	Clear.
2 "	0.5 "	1.5 "	6.25 "	Clear.	"	"	"
2 "	0.6 "	1.4 "	7.5 "	"	"	"	"
2 "	0.7 "	1.3 "	8.7 "	"	"	"	"
2 "	0.8 "	1.2 "	10.0 "	"	"	"	"
2 "	1.0 "	1.0 "	12.5 "	"	"	"	"

Magnus-Levy states that by diluting the clear solution, containing an excess of urea, with water, the albumin is precipitated even at ordinary temperatures. This observation I was unable to verify in my case. After the addition of two to three times the amount of water, at least, no turbidity was noted, even on the application of heat.

In attempting to ascertain the effect of urea upon the coagulation point it was only possible to note the first appearance of a turbidity, about the maximum turbidity, about the beginning of clearing, and roughly the point of maximum clearing. A flocculent precipitate was not obtained in these experiments.

Urine (neutral).	Water.	Urea solution (50 per ct.).	First turbidity.	Maximum turbidity.	First clearing.	Maximum clearing.
2 c.c.	2 c.c.	0.0 c.c.	58.5°	60.0°	79.0°	92.0°
2 "	1.8 "	0.2 "	58.0	60.0	75.0	92.0
2 "	1.6 "	0.4 "	58.0 (?)	Clear.	Clear.	Clear.

Like Magnus-Levy, I observed that the addition of a moderate excess of urea will dissolve the precipitate which has been produced by heat, even at ordinary temperatures, though at times this did not occur, for reasons which were not apparent.

Limits of Precipitation with Ammonium Sulphate. For purposes of comparison with other albuminous substances, the limits of precipitation with ammonium sulphate were determined both in the native urine and in a dialyzed specimen of the isolated substance according to Hofmeister's method, as described by Pick.[1] To this end a series of test-tubes was prepared, such that each contained 2 c.c. of the urine (viz., the dialyzed specimen) and an increasing amount of a saturated solution of ammonium sulphate, the mixture in each case being diluted with distilled water to 10 c.c. The concentration at which the first permanent turbidity occurred was regarded as the lower limit. The mixture in

[1] E. Pick. Untersuchungen über die Proteinstoffe, Zeit. f. phys. Chem., vol. xxiv. p. 246.

every case was thoroughly agitated, usually allowed to stand for one-half hour and then passed through a double filter; but at times it was necessary to wait for several hours (sometimes for twenty-four hours). To the clear filtrate of each tube 0.2 c.c. of the salt solution was then further added, in order to ascertain whether all of the substance had been precipitated. The concentration of the first specimen in which a further turbidity no longer occurred indicated the upper limit of precipitation. The results which were obtained in the case of the native urine were 0.7 and 4.2, and with a solution of the isolated substance 2.3 and 3.8, respectively.

Behavior on Digestion with Pepsin-hydrochloric Acid. To test the behavior of the albumin on peptic digestion a series of experiments was undertaken. The substance was previously isolated either by precipitation with ammonium sulphate or with alcohol, and purified as described. In some cases the solid substance was used, in others a solution. The degree of acidity of the digestive mixture corresponded to from 0.3 to 0.4 per cent. of hydrochloric acid. The pepsin used was a preparation of Merck's. Examination showed that this was suitable for our purposes. It was clearly soluble in water, gave only a faint biuret reaction, and, treated with an equal volume of a saturated solution of ammonium sulphate, a very faint turbidity. The digestive mixture was kept at a temperature of from 35° C. to 40° C. for a varying length of time. In the first experiment digestion was allowed to continue for a week. At the expiration of this time a thin deposit of an amorphous substance had appeared, of the nature of which nothing could be ascertained. The liquid was filtered and the filtrate neutralized. A precipitate did not occur. The solution was then acidified with acetic acid and treated with an equal volume of a saturated solution of sodium chloride and boiled. The clear filtrate was then treated with an equal volume of a saturated solution of ammonium sulphate, but after standing for nearly seventy-two hours a precipitate had not formed. There was merely a slight turbidity, which could not be removed by filtration. The solution was now further treated with the ammonium sulphate solution to the extent of one-half of the total volume, but again no precipitate resulted, even on standing four times twenty-four hours. The liquid had become somewhat more turbid, but could not be cleared on filtration. It was then saturated with the salt in substance. On standing a gummy material separated out, which manifestly represented the deutero-albumose B of Pick. The substance gave an intense purplish-red biuret reaction and a positive sulphur reaction (at first a brown color, later a precipitate of black sulphide of lead). The reaction of Adamkiewicz was positive, while Molisch's reaction was negative. Dilute copper sulphate solution caused no precipitation. On digestion with trypsin much tyrosin and comparatively little leucin were obtained.

After separation of the deutero-albumose B the clear filtrate was treated with one-tenth its volume of a very dilute solution of sulphuric acid saturated with ammonium sulphate—such that the reaction was feebly but distinctly acid. On standing even for several days a precipitate could not be obtained; only a slight turbidity resulted, which could not be removed by filtration. Deutero-albumose C, if present at all, was hence only formed in traces. On treating the filtered solution with Lugol's solution saturated with ammonium sulphate, a precipitate

formed, which on standing appeared as a gummy, black mass that closely adhered to the walls of the vessel. This was soluble in alcohol, and represents Pick's peptone B. A substance corresponding to Pick's peptone A was present, if at all, only in traces.

In the above experiments no evidence of the formation of primary albumoses was obtained; and as Magnus-Levy claims to have isolated a proto-albumose among the products of peptic digestion in his case, I repeated the experiment, allowing the digestion to continue for only twenty-four hours. The preparation used for this purpose was obtained by precipitation with alcohol, and was placed in the digestive mixture in the solid state. After twenty-four hours a small amount of an amorphous sediment was observed, as in the first instance, but it was likewise insufficient in amount for purposes of special examination. On neutralization no precipitate appeared. On the contrary, the liquid, which was distinctly turbid even after filtration, became almost clear as the neutral point was reached. It was then acidified by the addition of a couple of drops of acetic acid, and it was noted that on the addition of each drop a slight turbidity resulted, which disappeared on shaking. The solution was then treated with an equal volume of a saturated solution of sodium chloride. Upon the application of heat a beginning turbidity was noted between 52° C. and 53° C. This reached its height between 58° C. and 60° C., and was replaced between 78° C. and 80° C. by a cloudy, flocculent precipitate which became finely flocculent on boiling, but did not disappear. On cooling, what appeared to be an undigested portion of the Bence Jones albumin was filtered off, the filtrate neutralized, and further treated as described above. In this case, also, deutero-albumose B was obtained in considerable amount, while both deutero-albumose A and C were present only in traces.

As in this case, also, primary albumoses were not obtained, a third series of experiments was undertaken in which digestion was interrupted after from six to ten hours. About 10 grammes of the carefully purified substance were used and placed in the digestive mixture *en masse*. The process of "digestion" was closely followed and interrupted as soon as all the material had passed into solution. My special aim in these experiments was to separate from each other the undigested portion of the Bence Jones substance and any primary albumoses that may have been formed. To this end I first proceeded as described, viz., the solution was neutralized (no precipitation occurred) and then concentrated to a smaller volume. As in my case, the limits of precipitation of the substance were such that a satisfactory separation of the original substance from primary albumoses by fractional precipitation with ammonium sulphate was not possible, as in Magnus-Levy's case, I was forced to resort to some other plan. After a number of trials it was found that this separation could be readily effected by alcohol. It has been found that the Bence Jones substance could be completely precipitated by adding two volumes of alcohol (95 per cent.), and Pick[1] has shown that proto-albumose is soluble in alcohol of less than 80 per cent., while hetero-albumose is thrown down already in the presence of from 25 to 32 per cent. I accordingly precipitated the neutral digestive solution with an equal volume of a saturated solution

[1] E. P. Pick. Zur Kenntniss d. peptischen Spaltungsprodukte d. Fibrins, Pt. I., Zeitsch. f. physiol. Chem., 1899, vol. xxviii. p. 219.

of ammonium sulphate and allowed the mixture to stand for forty-eight hours. The fairly abundant precipitate which had collected by that time was then filtered off, washed with a small amount of iced water, stirred up with water at an ordinary temperature, and the resulting solution treated with twice its volume of 94 to 95 per cent. alcohol. The mixture was then allowed to stand for at least twenty-four hours. Any undigested portion of the Bence Jones substance—and I must confess that I did not find that it was digested so very rapidly as the statements in the literature led me to believe, although it *dissolved* comparatively rapidly—was thus thrown down and could readily be filtered off. The clear alcoholic filtrate was freed from alcohol by distillation in the vacuum. There remained a *clear* solution, which gave all the reactions of proto-albumose, and which could scarcely contain any other substance. A hetero-albumose was certainly not present in this fraction. Its absence in the alcoholic precipitate also was proved in another series of experiments by fractional precipitation with alcohol. On boiling the filtered alcoholic solution, moreover, the occurrence of a turbidity was never observed if care had been taken to allow the solution to stand sufficiently long so that everything that could be precipitated by alcohol in the cold had separated out.

In this manner, then, *the formation of proto-albumose from the Bence Jones substance could be satisfactorily demonstrated.* The amount of proto-albumose which was obtained was never large, but manifestly much more abundant than the amount of fraction I which Umber[1] could isolate among the digestive products of serum-albumin, of which he writes that it was always present in such small amounts, that it only appears as a faint opalescence on treating the digestive mixture with an equal volume of the sulphate solution, no matter whether the attempt was made to isolate it after three or not until after eighteen hours. He adds: "It would thus seem as though the fraction by no means represented a transitory stage for all following albumoses, which are present in abundance, unless, indeed, it is further decomposed already in *status nascendi.*" This observation I regard as important, in view of the fact that, as I shall show later on, the Bence Jones substance is in all probability a globulin, or at least closely related to the class.

After precipitation of the proto-albumose, together with the undigested portion of the original substance, by ammonium sulphate and their separation by filtration, the filtrate was then further treated as described, and with the same results. Deutero-albumose B and peptone B were always obtained in a fairly large amount. Deutero-albumose A also could be isolated in amounts sufficient to establish its identity; but of deutero-albumose C and peptone B only traces could be found, if, indeed, peptone B was present at all.

Crystallization. I have made a number of attempts to obtain the substance in crystalline form, but have thus far not been successful. I have noted, however, like others, that the granular-looking sediment which collects at the bottom of the vessel when the substance has been slowly precipitated by heating is composed of typical spheroliths, such as Hofmeister describes.

[1] F. Umber. Die Spaltung d. krystallinischen Eier und Serumalbumins sowie d. Serumglobulins durch Pepsinverdauung, Zeitsch. f. physiol. Chem., 1898, vol. xxv. p. 258.

While I was about to finish my work on the present case, and was surveying the literature on "Bence Jones' albumosuria," Dr. Edward S. Wood, of Harvard University, very kindly presented me with about 50 grammes of the isolated substance, for comparison, which he had obtained from the urine of Dr. Fitz's second case, and which was reported by Wright (see below). In this case, also, the diagnosis of multiple myeloma was made during the life of the patient and confirmed by autopsy. Dr. Wood wrote me that the substance had precipitated at a temperature between 50° C. and 60° C., but dissolved by heating to boiling, and precipitated again on cooling. It contained 0.2 per cent. of phosphorus, and owing to this observation, no doubt, Dr. Wood regarded the substance as a nucleo-albumose. Elementary analysis gave the following results, which, together with those obtained by other observers, I have placed in the accompanying table:

	C	H	N	O	S	P
Bence Jones	52.04	7.08	15.02	.....	1.09	0.19
Kühne	52.13	6.83	16.0			
Neumeister	52.87	6.91	15.55	.....	1.12	0.0
Magnus-Levy	.....	.....	15.56	.....	.....	0.0
Wood	42.3	7.72	13.85	35.76	0.16	0.21

The product which Dr. Wood used for elementary analysis was prepared by precipitating the urine with 95 per cent. alcohol, filtering, and reprecipitating with alcohol. This process was repeated at least three times, the alcohol being allowed to act upon the precipitate for several days at each time. The final purified product was dried over sulphuric acid in a vacuum to a constant weight. Comparison with the figures obtained by others suggests that even so the product was not quite pure, and I have succeeded, as a matter of fact, in obtaining it free from phosphorus by appropriate treatment.

Dr. Wood further writes me that he obtained the same substance from the diseased portion of the bone tissue, but that he could not obtain it from the bone-marrow in any other portion of the body of the patient.

The material which I received for examination had been isolated by precipitation with alcohol, and appeared as a white, pasty mass, which on prolonged standing dissolved in water, but much more readily in very dilute ammonia (0.5 to 0.25 per cent.). This solution remained clear on subsequent neutralization; on heating a turbidity appeared between 50° C. and 55° C., which cleared on boiling and reappeared on cooling. The behavior toward dilute ammonia showed that the product was not contaminated by the common albumins which may occur in the urine. Like my own substance, this also could be precipitated from its neutral solutions by salting with magnesium sulphate to saturation, and it was noted that the precipitate was soluble in water. With rock salt partial precipitation also occurred, and in this case the precipitate was likewise soluble in water. The limits of precipitation with ammonium sulphate were 1.7 and 2.8, respectively. On digestion with pepsin-hydrochloric acid a proto-albumose was formed which

could be precipitated by one-half saturation with ammonium sulphate, and which was soluble in 66 per cent. alcohol. A hetero-albumose could not be demonstrated; but, as in the first instance, I also obtained the three deutero-albumoses A, B, and C, and the two peptones A and B, though of these the deutero-albumose B and peptone B were the only products that were present in large amounts.

SUMMARY OF REPORTED CASES. It had been my intention to present a more detailed account of the various cases of Bence Jones' "albumosuria" that have been reported in the literature, but it was found that such an analysis would have occupied more space than was available. I therefore abandoned the idea, and have below merely arranged the reported cases in chronological order, together with the necessary references and the anatomical diagnosis whenever a record of an autopsy could be found.

The *first case* occurred in the practice of Drs. Watson and MacIntire, and was reported by Bence Jones,[1] in 1847, before the Royal Society of London. A clinical report of the case by MacIntire followed in 1850. The post-mortem diagnosis was "osteomalacia fragilis rubra."

The *second case* occurred in the practice of M. Doornik, of Amsterdam, in 1869, and was apparently also seen by Stokvis, who examined the urine. The clinical diagnosis in this case also was osteomalacia, but a post-mortem examination was not made. The urine was studied in detail by Kühne,[2] who published his results in 1883.

The *third case* was described from the clinical stand-point by Kahler in 1889. The clinical diagnosis in his case also had been osteomalacia, but post-mortem multiple myeloma was discovered. Kahler suggested that had a detailed microscopical examination been made in the two other cases it might have been found that they also were in reality cases of multiple myeloma which clinically simulated osteomalacia. He expressed the opinion that the presence of Bence Jones' "albumose" might possibly be of service in the diagnosis of multiple myeloma from osteomalacia. The urine in Kahler's case was examined by Huppert.[3]

The *fourth case* occurred in the service of Stokvis,[4] of Amsterdam. A preliminary report appeared in 1891. A more detailed account of the case was given by Ribbink in 1892, and in 1893 Zeehuisen published his report of the autopsy together with the chemical examination

[1] H. Bence Jones. Philos. Trans. Royal Soc., 1848, Pt. I. p. 55. W. MacIntire, Med. Chir. Trans., London, 1850, vol. xxxiii. p. 211.

[2] W. Kühne and R. H. Chittenden. Ueber die nächsten Spaltungsprodukte d. Eiweisskorper, Zeit. f. Biol., 1883, vol. xix. p. 198. W. Kühne, Ueber Hemialbumose in Harn, ibid., p. 209. W. Kühne and R. H. Chittenden, Ueber Albumosen, ibid., 1884, vol. xx. p. 40.

[3] Huppert. Ueber einen Fall von Albumosurie, Prag. med. Woch., 1889, vol. xiv. p. 35.

[4] B. I. Stokvis. Ueber Hemialbumosurie, Nederl. Tijdschrift voor Geneesk., 1891, vol. ii. p. 36, cit. in Maly's Jahresb., 1892, vol. xxi. p. 412. H. C. G. Ribbink, Een geval v. Albumosurie, Diss. Amsterdam, 1892, cit. in Maly's Jahresber., 1893, vol. xxii. p. 525. H. Zeehuisen, Nederl. Tijdschr. v. Geneesk., 1893, Pt. I. p. 829, cit. in Maly's Jahresber., 1894, vol. xxiii. p. 577.

of the diseased tissues. The anatomical diagnosis was osteosarcomatosis (myeloma).

The *fifth case* occurred in Stintzing's clinic in 1895. The clinical history, together with an account of some experiments regarding the general metabolism of the patient, is reported by Seegelken.[1] The study of the urine was made by Matthes in Neumeister's laboratory. Post-mortem examination revealed the existence of multiple myeloma.

The *sixth case* occurred in the clinic of Senator,[2] who has reported the history of the patient in detail. A general account of the patient's urine is given by Rosin, while a more detailed study appears in Süssmann's thesis of 1897 (Leipzig). Post-mortem myelogenous round-celled sarcomatosis (myeloma) of the ribs was found.

The *seventh case* is reported by Bozzolo[3] under the interesting title "Sulla malattia di Kahler." The urine was examined by Belfanti. An autopsy could not be made, but it is quite clear from the detailed clinical account which is given that this patient also was the subject of multiple myeloma.

The *eighth case* is reported by Ewald.[4] During the life of the patient the diagnosis of myeloma was made upon the basis of a histological examination of a growth of the right clavicle which was removed at an operation.

The *ninth case* occurred in Lichtheim's clinic, and is reported by Ellinger.[5] The anatomical diagnosis was multiple lymphoma (myeloma) and lymphoid infiltration of the bone-marrow of the ribs, the vertebræ, and sternum.

The *tenth case* was briefly reported by Naunyn,[6] in 1898, at a meeting of the "Unter-Elsässischer Aerzteverein," in Strassburg (January 29, 1898). He expressed the opinion that in this case, also, multiple myeloma of the bones of the thoracic skeleton existed, but an autopsy was not made. The urine was studied in detail by Magnus-Levy.

[1] Seegelken. Ueber multiples Myelom u. Stoffwechseluntersuchungen b. demselben, Deut. Arch. f. klin. Med., 1897, vol. lviii. p. 276. M. Matthes, Ueber Eiweisskörper im Urine b. Osteomalacie, Verhandl. des XIV. Cong. f. inn. Med., 1896, p. 476. R. Neumeister, Lehrbuch. d. physiol. Chem., 1897, 2d ed., p. 806.

[2] H. Senator. Asthenische Lähmung, Albumosurie u. multiple Myelome, Berl. klin. Woch., 1899, vol. xxxvi. p. 161. H. Rosin, Ueber einen eigenartigen Eiweisskörper im Harn, u. seine diagnostische Bedeutung, Berl. klin. Woch., 1897, vol. xxxiv. p. 1044.

[3] Bozzolo. Sulla malattia di Kahler, La Clinica medica Italiana, 1898, cit. in Centralbl. f. d. med. Wiss., 1898, vol. xxxvi. p. 572. The case was first reported in 1897 before the Eighth Congress of International Medicine.

[4] K. Ewald. Ein chirurgisch interessanter Fall v. Myelom., Wien. klin. Woch., 1897, vol. x. p. 169.

[5] A. Ellinger. Das Vorkommen des Bence Jones'schen Körpers im Harn bei Tumoren d. Knochenmarkes u. seine diagnostische Bedeutung, Diss. Königsberg, 1898, and Deutsch. Arch. f. Klin. Med., 1899, vol. lxii. p. 255.

[6] Naunyn. Ein Fall v. Albumosurie, Deutsch. med. Woch., 1898; Vereins Beilage, No. 30, p. 217. Magnus-Levy, Ueber d. Bence Jones'schen Eiweisskörper, Zeitschr. f. physiol. Chem., 1900, vol. xxx. p. 200.

The *eleventh case* was briefly reported by Bradshaw[1] before the Royal Medical and Chirurgical Society, April 26, 1898. A further report appeared in 1900. No record of an autopsy is given, but Bradshaw regards the case as an unmistakable instance of bone disease and probably of myelomata.

The *twelfth case* is reported by Fitz.[2] The clinical diagnosis was myxœdema, and there was no clinical evidence of bone disease. The patient died while under treatment with thyroid extract. Unfortunately, an autopsy could not be held. The urine was examined by Dr. E. S. Wood.

The *thirteenth case* also was under the care of Dr. Fitz,[3] and is briefly referred to in his previous paper, where he speaks of the patient as being then under the charge of Dr. F. C. Shattuck. An account of the clinical history of the case and a study of the post-mortem findings is given by Wright. The urine in this case also was examined by Dr. E. S. Wood, and through the latter's courtesy I was enabled to study the isolated substance. (See above.)

The *fourteenth case* is reported by Vladimir de Holstein,[4] in 1898. In this case the diagnosis "multiple myelomatosis" was made during the life of the patient on the basis of the existing "albumosuria." In a subsequent note it is stated that the clinical diagnosis was confirmed by autopsy. A detailed examination of the urine is wanting.

The *fifteenth case* is reported by Buchstab and Schaposchnikoff.[5] The original diagnosis had been pseudoleukæmia, but after Bence Jones' "albumose" was found in the urine it was changed to myeloma. This was confirmed by autopsy.

The *sixteenth case* occurred in the clinic of Lichtheim, and was reported by Askanazy[6] before the Verein f. Wissenschaftliche Heilkunde, in Königsberg (Prussia), at the meeting of January 23, 1899. A more detailed account of the case appeared in 1900. Post-mortem examination showed the existence of lymphatic leukæmia, with the corresponding characteristic changes in the bone-marrow.

[1] T. R. Bradshaw. A Case of Albumosuria, Brit. Med. Journ., 1898, Pt. I. p. 1136. Myelopathic Albumosuria, ibid., November 3, 1900.

[2] R. H. Fitz. The Significance of Albumosuria in Medical Practice, THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, 1898, vol. cxvi. p. 30.

[3] THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, ibid., p. 43. J. H. Wright, A Case of Multiple Myeloma, Journ. of the Boston Soc. of Med. Sci., 1900, vol. iv. p. 195, and Contributions to the Science of Medicine, W. H. Welch Memorial Vol., Johns Hopkins Press, 1900, p. 359.

[4] Vladimir de Holstein. Semaine Médicale, 1898, p. 206, and ibid., 1899, p. 83.

[5] L. Buchstab and B. Schaposchnikoff. Ein Fall von diffusem Myeloma d. Knochen in Zusammenhange mit einer typischen Albumosurie als einem charakteristischen diagnostischen Merkmale. Russ., Arch. f. Pathol., klin. Med. und Bacteriol., 1899, vol vii. p. 11, Russian.

[6] S. Askanazy. Ueber die diagnostische Bedeutung d. Bence Jones'schen Albumosurie, Deutsch. med. Woch., 1899, vol. xxv. V. B. p. 177, and Deutsch. Arch. f. klin. Med., 1900, vol. lxviii. p. 34.

The *seventeenth case* is briefly described by Sternberg,[1] in 1899. An autopsy was not made. In the urine large amounts of the Bence Jones substance were found (examination by E. Freund). An account of the reactions of the body, however, is not given.

The *eighteenth case* is the one under present consideration. A preliminary report was made by Dr. Hamburger[2] before the meeting of the Johns Hopkins Medical Society on November 5, 1900. The clinical diagnosis, as I have said, was multiple myeloma, but an autopsy, unfortunately, could not be made.

The *nineteenth case* occurred in the service of Dr. Osler, and is likewise reported by Hamburger.[3] Autopsy revealed myelomata in the skull, left scapula, both clavicles, the sternum, the right ilium, and neck of the right femur. A detailed report of the post-mortem findings is given by MacCallum.[4]

The *twentieth case* is reported by Kalischer.[5] Post-mortem examination revealed lymphoid hyperplasia of the marrow of the ribs (myeloma). (Examination by Dr. Franz Müller.)

The *twenty-first case* is briefly referred to by Rostoski.[6] An account of the clinical history or of a post-mortem examination is not given.

The *twenty-second case*, finally, is reported by Jochmann and Schumm.[7] The writers make no mention of any of the cases that have been reported since 1897, with the exception of a supplementary note on the preceding case. They claim that their case is the first true instance of osteomalacia and not of multiple myeloma, in which the Bence Jones substance was found in the urine. Autopsy showed involvement of the vertebræ, the ribs, sternum, pelvic bones, and long bones. In addition, interstitial and parenchymatous nephritis was noted, with slight amyloid degeneration.

The above twenty-two cases are the only ones recorded in the literature in which the presence in the urine of the Bence Jones substance has been definitely established. It will be noted that, barring those in which no autopsy was made, and assuming, with Kahler, that Bence Jones' case was probably myeloma and not osteomalacia, myeloma actually existed in thirteen. The relation between the two conditions in so large a percentage of cases suggested the possibility that the substance may possibly have been present in still other cases of myeloma

[1] M. Sternberg. Vegetationsstörungen und Systemerkrankungen der Knochen, Nothnagel's Pathol. und Therap., 1899, vol. vii., pt. 2, sec. 2, p. 57.

[2] L. P. Hamburger. Loc. cit.

[3] Loc. cit.

[4] W. G. MacCallum. A Case of Multiple Myeloma, Journ. Exper. Med., 1901, vol. vi. p. 53.

[5] S. Kalischer. Ein Fall v. Ausscheidung d. Bence Jones'schen Eiweisskörper durch d. Urin bei Rippenmyelomen, Deutsch. med. Woch., 1901, vol. xxvii. p. 54.

[6] Rostoski. Albumosurie und Peptonurie, Münch. med. Woch., 1901, vol. xlviii. p. 1115. Proceedings of the Physikalisch-medicinische Gesellsch. v. Würzburg, meeting of June 13, 1901.

[7] G. Jochmann und O. Schumm. Typische Albumosurie bei Osteomalacie, Münch. Med. Woch., 1901, vol. xlviii. p. 1340.

also, but may not have been recognized as such. Unfortunately, the term myeloma is not applied to a definite clinical picture, nor even to a uniform pathological-histological condition, so that I was much embarrassed in my search of the literature in deciding what cases of apparent malignant disease of the bones belonged to this category. I was greatly aided, however, by the data given in Wieland's[1] excellent paper, although the writer's interpretation of some of our cases in which the Bence Jones subtance was found in the urine is at variance with the diagnosis originally made. The cases which Wieland accepts as cases of true myeloma, in addition to the thirteen already referred to, are those of v. Rustitzky,[2] Zahn,[3] and Klebs,[4] even more probably that of Weber,[5] possibly the case of Marchand,[6] and perhaps also those of Winkler[7] and Funkenstein.[8] Markwald's[9] case, which was formerly regarded as an instance of myeloma, is now classified as endothelioma. I have gone over the original report of the case, together with the true myeloma cases, however, notwithstanding, as it was very similar to that of Kahler,[10] in which the Bence Jones substance was actually found. My search, however, has not led to the discovery of a new, well-defined case of Bence Jones' "albumosuria." Zahn, it is true, reports that in his case albumin was always present in variable amounts, and post mortem no definite lesion of the kidneys was found. A more detailed account of the reactions, however, is lacking. v. Rustitzky, Weber, Winkler, and Markwald remark that in their cases no albumin was present in the urine, and v. Jaksch[11] further states that in one case of myeloma which he observed the Bence Jones albumin could at no time be demonstrated. Marchand makes no note of a urinary examination whatever. As a result we are forced to the conclusion that while the Bence Jones albumin may be present in association with myeloma, this is not necessarily the case. There is some evidence to show, moreover, that the substance may occur in other diseases affecting the bone-marrow as well. I have thus pointed out that in Jochmann and Schumm's case post-mortem examination revealed the existence of osteomalacia, and in Askanazy's case of lymphatic leukæmia (lymphadenoid degeneration

[1] E. Wieland. Studien über das primär multiple auftretende Lymphosarcom der Knochen. Virchow's Arch., 1901, vol. clxvi. p. 103.

[2] v. Rustitzky. Multiples Myelom. Deutsch. Zeitsch. f. Chirurg., 1873, vol. iii.

[3] F. W. Zahn. Ueber das multiple Myelom, seine Stellung im onkologischen System u. seine Beziehung zur Anæmia lymphatica, Deutsch. Arch. f. Chirur., 1885, vol. xxii.

[4] Klebs. Die allgem. Pathol., 1889, Pt. 2.

[5] Weber. General Lymphadenomatosis of Bones, One Form of "Multiple Myeloma," Journ. of Pathol. and Bacter., 1898, p. 59.

[6] Marchand. Ein Fall von seniler Osteomalacie, Berlin. klin. Woch., 1889, No. 29, p. 486.

[7] Winkler. Das Myelom. in anatom. u. klin. Beziehung, Virchow's Arch., 1900, vol. clxi. p. 252.

[8] O. Funkenstein. Ein Fall von multiplem Myelom, Inaug. Diss, Strasburg, 1900.

[9] Markwald. Ein Fall von multiplem, intervasculärem Endotheliom in d. gesammten Knochen d. Skelets, Virchow's Arch., 1895, vol. cxli. p. 128.

[10] Loc. cit.

[11] v. Jaksch. Verhandl. d. 18th Cong. f. inn. Med., 1900, p. 500.

of the bone-marrow). A detailed report of the post-mortem findings in Jochmann's case has not as yet appeared; but if future investigations should prove that their case was actually one of osteomalacia, the observation would gain in interest, as other observers have heretofore not found the substance in the disease in question, although diligent search has been made. Bence Jones himself thus writes to Kühne that he examined the urine of a fairly large number of well-marked cases (from 1845 to 1869), but that he could not find the substance again.

Stokvis, also, has not a single instance to report where Bence Jones' "albumosuria" was associated with osteomalacia, and v. Jaksch[1] states that he never found "albumose" in the urine in numerous cases of the disease. The only other observations which I have been able to find in the literature in which it is claimed that "albumoses" were present in the disease in question are the cases of Langendorff-Mommsen[2] and of Raschkes.[3] In neither case, however, is there sufficient evidence to show that the urine actually contained the Bence Jones substance, although the reactions described by Raschkes suggest it rather more strongly than in the first case.

In association with other multiple new-growths affecting the bones, excepting myeloma, the substance in question has apparently not been found, unless, indeed, some of the cases which have been reported under the title "myeloma" are, as Wieland and others suggest, not cases of true myeloma. Into this question, however, I can scarcely enter at this place. Suffice it to say that an analysis of the reported cases of multiple tumors affecting the bones, which I have made with a view of possibly discovering some overlooked instance of "albumosuria," led to no result. Runeberg,[4] it is true, reports that in his case the urine contained *much* albumin, and at the autopsy it was noted that in the spongy portion of the sternum, the ribs, the vertebræ, and the sacrum there was a marked hyperplasia of granular, light yellow, nucleated cells, as also a large number of "giant cells." Runeberg states that the urine contained numerous hyaline and finely granular casts, and adds that the finding of the latter alone speaks against a true inflammatory disease of the kidneys. The existence of cirrhotic kidneys, moreover, was excluded, and at the post-mortem it could be definitely shown that a nephritis did not exist. From the account given the possibility thus suggests itself that in this case the "albu-

[1] R. v. Jaksch. Klinische Diagnostik, 1896, Wien u. Leipzig.

[2] O. Langendorff and J. Mommsen. Beiträge zur Kenntniss d. Osteomalacie, Virchow's Arch., 1877, vol. xlix. p. 649.

[3] A. Raschkes. Ein Fall von seniler Osteomalacie mit Albumosurie, Prag. med. Woch., 1894, vol. xix. p. 649.

[4] J. W. Runeberg. Ein Fall von medullärer Pseudoleukæmie, Deutsch. Arch., 1883, vol. xxxiii. p. 629.

mose" may have been present, but a definite conclusion can scarcely be reached in the absence of a more detailed examination.

The negative cases, in regard to which I consulted the original histories, are those reported by Lannelongue,[1] Arnold,[2] Litten,[3] Grawitz,[4] Waldstein,[5] Hammer,[6] Wieland,[7] Kudrewetzky,[8] and Nothnagel.[9]

In cases of multiple metastatic carcinoma involving the bones "albumosuria" never occurs.

The only instance of bone disease other than what has been described above, in which a substance has been encountered in the urine of man, which may be interpreted as being identical with the body under consideration, is a case of tubercular osteo-arthritis of the shoulder that has been briefly reported by Vidal[10] before the Société de Biologie of Paris (October 29, 1898). The patient died of acute pleuro-peritoneal tuberculosis, but an autopsy was apparently not held. The reactions which were obtained from the patient's urine, and from which Vidal himself concludes that the substance must have belonged to the "primary proteoses," are the following: After the addition of a few drops of acetic acid no precipitate results on boiling. A well-marked biuret reaction is obtained. Cold nitric acid produces a milky turbidity, which disappears on boiling and reappears on cooling.[11]

It is stated by Laache[12] and Lussana[13] that in pernicious anæmia "peptonuria," in the older meaning of the term, is of common occurrence; but I have not been able to find any data in the literature to warrant the conclusion that the "peptone" in such cases is identical with the Bence Jones albumin. The statement, however, is of interest, as it is a well-known fact that myeloma may follow a clinical course which is quite similar to the common form of pernicious anæmia. A

[1] Lannelongue. Gaz. des Hôpit., Nos. 41 and 42.

[2] Arnold. Drei Fälle v. primärem Sarcom d. Schädels, Virchow's Arch., 1873, vol. lvii. p. 297.

[3] Litten. Ueber einen in medulläre Leukæmie übergehenden Fall v. primärer Anæmie. Berlin. klin. Woch., 1877, Nos. 19 and 20.

[4] P. Grawitz. Maligne Osteomyelitis u. sarcomatöse Erkrankungen d. Knochensystems als Befunde b. Fällen v. perniciöser Anæmie, Virchow's Arch., 1879, vol. lxxvii. p. 353.

[5] L. Waldstein. Ein Fall von progressiver Anæmie u. darauffolgender Leucocythæmie mit Knochenmarkerkrankungen u. einem sogenannten Chlorom (Chlorolymphom), Virchow's Arch., 1883, vol. xci. p. 12.

[6] Hammer. Primäre sarcomatöse Ostitis mit chronischem Rückfallsfieber, Virchow's Arch., 1894, vol. cxxxvii. p. 280.

[7] Wieland. Loc. cit.

[8] B. Kudrewetzky. Zur Lehre v. d. durch Wirbelsäulen Tumoren bedingten Compressions, Erkrankung d. Rückenmarks, Zeitsch. f. Heilkunde, 1892, vol. xiii.

[9] H. Nothnagel. Ueber eine eigenthümliche perniciösen kockenerkrankung. (Lymphadenia ossium), Virchow's Festschrift, 1891, vol. ii. p. 155.

[10] E. Vidal. Note sur un cas d'albumosurie, Compt. rend. de la Soc. de biol., 1898, vol. l., p. 991.

[11] I find that another case is briefly reported in which the Bence Jones substance was apparently present in the urine. No details, however are given. Matthes, Verhandl. d. Congr. f. inner Med., 1900, p. 501.

[12] Laache. Die Anæmie. Christiania, 1883.

[13] Lussana. Cit. by Eichhorst, Perniciöse Anaemie, Eulenburg's Real-Encycl., 3d ed.

more careful search in this particular direction than I have been able to make may possibly unearth still other cases of Bence Jones' albuminuria.

From the reported cases of Bence Jones' albuminuria the conclusion may be drawn: 1. That the presence of the substance in the urine of man usually indicates the existence of multiple new-growths affecting the bones, and generally of myeloma. 2. That myeloma may apparently occur in the absence of the peculiar albuminous substance. 3. That the existence of the urinary condition in association with other diseases without involvement of the bones is not as yet proved by the report of any case in which a careful post-mortem examination has been made. 4. That malignant disease of the bones, in general, may exist in the absence of the Bence Jones albumin from the urine.

Outside of the urine, and possibly the blood and the tumor masses of the cases described in the foregoing pages, the Bence Jones albumin has apparently also been encountered in the urine of dogs during the continued administration of pyrodin (monoacethyl-phenylhydrazin). Zülzer[1] states that the "albumosurie" is practically a constant result of pyrodin poisoning in dogs, but that it only persists in its pure form for a very short time, and is soon obscured by the common form of albuminuria, which develops as the result of the inevitable nephritis. He cites one instance, however, in which the albumosuria persisted for four days, uncomplicated by albuminuria. With nitric acid a heavy precipitate occurred at ordinary temperatures, which dissolved entirely on heating. Similar results were obtained with sulpho-salicylic acid, picric acid, Almen's reagent, and acetic acid and potassium ferrocyanide. On heating the urine, after acidifying distinctly with acetic acid, a marked turbidity occurred between 50° C. and 60° C., which disappeared almost entirely on heating to 100° C. The isolated substance (precipitation with alcohol) gave the same reactions as the native urine. After drying it was soluble only in boiling water after the addition of a little soda. Millon's reaction, the biuret reaction, and the sulphur test were positive. On half saturation with salt a marked turbidity occurred (!).

A detailed account of the experiments is still lacking, but I conclude from Zülzer's paper that the "albumosuria" was associated with changes in the bones.

In Tallquist's[2] monograph on pyrodin-anæmia no mention is made of the occurrence of "albumosuria," but it is possible, as Zülzer suggests, that it has been overlooked, owing to the simultaneous presence of common albumin.

[1] G. Zülzer. Ueber experimentelle Bence Jones'sche Albumosurie, Berlin. klin. Woch., 1900, vol. xxxvii. p. 894.

[2] T. W. Tallquist. Ueber experimentelle Blutgift-Anaemien. Berlin, 1900. A. Hirschwald.

Whether or not the Bence Jones substance may also occur in normal bone-marrow, as is suggested by the experiments of Fleischer,[1] remains to be decided by future researches according to more modern methods. If so, it is apparently only present in traces. Larger amounts of a similar but apparently not identical substance were found by Virchow[2] in the bone-marrow of a patient dead with osteomalacia; and it has been stated by some that this was in reality the Bence Jones albumin. Virchow, however, has made no statement to this effect; and Kühne in speaking of this observation states that it merely shows "that common albumin after solution in acetic acid by boiling can give rise to a precipitate, on treating with nitric acid, which dissolves on heating and reappears on cooling." Fleischer's substance differs from that of Virchow in the fact that the precipitate caused by nitric acid dissolved upon the further addition of concentrated acetic acid.

Comparison of Results. *Amount.* On comparing my results with those obtained by others, and these in turn with each other, it is clear, I think, that all observers have been dealing with one and the same substance. They all mention that on treating the urine with nitric acid a precipitate results, which disappears on boiling and reappears on cooling. This reaction, it is true, is not characteristic of the Bence Jones substance, as it is also obtained with the deutero-albumoses which may occur in the urine under various other pathological conditions. But it should be borne in mind that whereas deutero-albumoses are usually only present in such small amounts that special methods are necessary for their demonstration, the Bence Jones substance generally occurs in quantities which are so large as to arrest attention at once. In the following table I have collected the results which have been obtained by the various observers:

Fitz	0.12 —	0.93	pro mille.
Ellinger	0.25 —	0.5	" "
Askanazy	0.5 —	1.25	" "
Fitz	0.1 —	2.25	" "
Huppert	3.0		" "
Fitz-Wright	3.3 —	3.4	" "
Kalischer	5.0 —	5.0	" "
Süssmann	6.0		" "
Hamburger, I.	6.0		" "
Matthes	4.0 —	6.0	" "
Simon	0.12 —	5.12	" "
Bozzolo	10.0		" "
Bradshaw	10.0		" "
Ribbink	20.0		" "
Magnus-Levy	18.0 —	24.0	" "
Bence Jones	67.0		" "
Noël Paton	70.0		" "

[1] R. Fleischer. Ueber das Vorkommen d. sogenannten Bence Jones'schen Eiweisskörper's im normalen Knochenmark, Virchow's Arch., 1880, vol. lxxx. p. 482.

[2] R. Virchow. Ueber parenchymatöse Entzündungen, Virchow's Arch., vol. iv. p. 308.

From this table it will be seen that in some cases the elimination of the substance far exceeds the largest amounts of common albumin that may be encountered in the urine.

Behavior on Heating. All observers agree that the albuminous substance in question begins to be precipitated from the urine at a temperature which is well below that at which serum albumin is coagulated, viz., between 50° C. and 58° C. Individual variations are undoubtedly referable to a varying degree of acidity and the amount of salt present, and may indeed occur in one and the same case. Kühne's is the only case in which the initial temperature of precipitation was found below 50° C., viz., at 43° C. Naunyn states that his substance was precipitated between 49° C. and 53° C. As regards the behavior of the urine on further heating, the statements of the various observers differ more radically. Kühne and Matthes thus find that in their cases the urine cleared entirely on boiling, and it appears that this also occurred in Ellinger's case, as the faint turbidity which remained at 100° C. was here no doubt referable to the contaminating nucleoalbumin. In Ribbink's case and those of Huppert, Rosin, Magnus-Levy, Rostosky, and myself, on the other hand, the urine did not clear on boiling. This apparent difference might suggest that the substance which the various investigators had under observation was not the same in all cases. Such a conclusion, however, is not admissible, in view of the fact that all possible variations in the solubility of the precipitate at 100° C. may be observed not only in the different cases, but even in one and the same instance. Naunyn thus reports that the precipitate which appeared between 49° C. and 53° C. cleared almost entirely on subsequent heating to boiling. Magnus-Levy, who studied the urine from the same patient later on, writes that at first a large portion of the precipitate dissolved on boiling, but that a considerable fraction remained undissolved; and still later in the course of the disease it was found that even with a neutral reaction the substance could be quantitatively precipitated by heat and remained insoluble on boiling. In my case, also, it was found that at first the urine became "clear" on boiling after previous precipitation; while later, when I had occasion to study the urine, a clearing at 100° C. could scarcely be noted with the eye. I have shown, moreover, that in my case, as in Magnus-Levy's, it was possible to *completely* precipitate the substance by heat if the elevation of temperature was carried out slowly, providing that a sufficient amount of salt was present and the urine presented an acid reaction. In such an event no solution whatever occurred on boiling. But, aside from these observations, the identity of the various substances is proved by the fact that, as Magnus-Levy first pointed out, it is possible to render the body soluble at 100° C., or insoluble, at will, by simple measures which in themselves can hardly be supposed to

change the chemical nature of the substance. A solution of the isolated substance, moreover, which has been rendered acid by acetic acid, and which contains a certain amount of salt, shows the "typical" behavior of the Bence Jones substance on heating as it was described by Kühne. Its insolubility at 100° C. in the urine must hence depend upon the associated presence of some other substance or substances in the urine, among which the salts, no doubt, are of prime but not of exclusive importance. What other factors are here of moment, however, is as yet unknown. Remembering the influence of the degree of acidity upon the phenomenon, it might be supposed that the relative amount of acid phosphates would enter into consideration, but this does not seem to be the case. Using two different mixtures of monopotassium phosphate and disodium phosphate in solution, of which the one was strongly alkaline, while the other was markedly acid, and adding varying amounts of these solutions to a given amount of a solution of the Bence Jones substance, Magnus-Levy was unable to obtain any effect whatever upon the coagulability of the body. He showed, however, that the addition of ammonium chloride in a definite proportion (½ per cent.) renders the substance more readily soluble at 100° C. after it has been previously coagulated, and that the addition of a certain amount of urea to the solution or to the urine may prevent heat coagulation altogether. These experiments I have repeated, and I have been able to confirm Magnus-Levy's results. I do not think, however, that the differing behavior of the urine, as noted by different observers, can be explained upon the basis of these observations alone. Other factors are here, no doubt, active, of the nature of which we are as yet in ignorance; and to the activity of such factors I have no doubt some other and minor variations in the behavior of the body that have been noted by different observers may be due. For such reasons, also, differing reactions may be obtained in one and the same case at different times. So much is certain, however, that it is no longer admissible to speak of the solubility of the coagulated substance at 100° C. as a characteristic and typical reaction, *so far as the urine is concerned. It is characteristic, however, of a solution of the isolated substance in the presence of a certain amount of acid and of salt. As the most characteristic general reaction, I should regard the coagulability of the substance at a temperature of from 50° C. to 58° C.*[1]

In the above pages I have repeatedly made use of the term *coagulation* in reference to the precipitation of the Bence Jones substance by

[1] Whether or not serum albumin was actually present in the urine in association with the Bence Jones substance as often as stated by individual observers I am not prepared to decide. I should suggest, however, that in the future a special examination in this direction be made. To conclude that the common albumins are present because the urine does not clear entirely on boiling is unwarrantable.

heat or on treating with alcohol. Strictly speaking, this term is not applicable, however, as it implies a material alteration of the chemical properties of the substance, which in reality has not been effected. It is true that such precipitates are practically insoluble in cold distilled water, but they dissolve with comparative ease in boiling water in the presence of a small amount of sodium carbonate, and, as Magnus-Levy has first pointed out, the alcohol precipitate is readily soluble in very dilute solutions of ammonia. On subsequent neutralization a solution is then obtained which behaves, on heating, as the original solution, if ammonium chloride is present to the extent of ½ per cent. The latter observation is especially important, as the common albumins which may occur in the urine are insoluble in dilute ammonia after having been precipitated by alcohol. The coagulate, moreover, is readily soluble in dilute acids, and from such solutions the substance is again thrown down upon the application of heat, providing that a certain amount of salt is present.

Dialysis. As regards the behavior of the substance on dialysis, all observers who have examined in this direction agree that it does not pass through parchment, with the exception of Ribbink, who states that a portion of his substance escaped in this manner. It is quite possible, however, that Ribbink's parchment was not altogether dense. Important in this connection is the fact that the substance is not precipitated from its solutions by dialysis, no matter how prolonged this may be.

Behavior on Salting with Sodium Chloride. Apparent differences are recorded in the behavior of the substance on salting with sodium chloride. Huppert reports that in his case the substance was completely precipitated from the urine by salting to saturation between 35° C. and 40° C. Ribbink, on the other hand, reports that even after standing for several days he was unable to obtain a precipitate by salting with rock salt at any temperature between 15° C. and 40° C. Matthes states that in his case only a fraction of the substance was precipitated by salting the urine to saturation, and then only on standing for several days. Süssmann and Magnus-Levy found that in their cases the substance could be partially precipitated from the acid urine in this manner, and Ellinger writes that on the addition of a saturated solution of sodium chloride he obtained a precipitate even at ordinary temperatures. Kühne, under the latter conditions, merely noted a turbidity. In my case no turbidity whatever occurred on treating the acid urine with a saturated solution of common salt, even when added in the proportion of 3 to 1. With an alkaline urine, however, that had undergone ammoniacal decomposition I found that a precipitate formed upon the addition of 0.4 c.c. of a saturated solution of salt to 2 c.c. of the urine. With rock salt partial precipitation occurred at ordinary tem-

peratures, while complete separation occurred on salting at from 35° C. to 40° C.

With a neutral solution of the isolated substance I very curiously found that partial precipitation occurred on salting with sodium chloride to saturation, whereas Magnus-Levy and Süssmann state that a neutral and purified solution of the body cannot be precipitated by salting with sodium chloride at ordinary temperatures. Magnus-Levy, however, has manifestly overlooked the fact that Kühne also found that his substance could be precipitated with sodium chloride from its neutral solutions. In his second communication he states distinctly that a solution of the isolated substance gave a copious precipitate upon the addition of rock salt prisms in acid, as well as in neutral and feebly alkaline solutions. The precipitate, moreover, was soluble in water.[1]

These data in themselves suffice to show that the question, whether or not the Bence Jones substance can be precipitated on salting with sodium chloride, depends not only upon the reaction of the solution, but upon other factors as well, which are as yet but little understood.

The observation of Huppert, who succeeded in completely precipitating his substance from the urine by salting to saturation at a temperature between 35° C. and 40° C., may be explained by the assumption that this precipitation is not a true salt precipitation at all, but an actual coagulation, which, owing to the presence of so large an amount of salt occurs at a much lower temperature. I have accordingly also found that the precipitate, which I obtained on salting with rock salt to saturation at a temperature of about 37° C., was insoluble in water.

Limits of Precipitation with Ammonium Sulphate. The differences in the limits of precipitation with ammonium sulphate which exist between Magnus-Levy's case, Ellinger's, Fitz's No. 2, and my own are possibly owing to differences in the amount of salts which were originally present in the urine, to varying strengths of the albuminous solutions, and like factors. On this basis, at any rate, it would scarcely be warrantable to assume that each of us was dealing with a different substance.

Ellinger (solution of isolated substance, previously coagulated and dissolved in a dilute solution of sodium carbonate)	2.0 and 4.0
Magnus-Levy (similar preparation, but subsequently neutralized) .	0.6 " 2.2
Magnus-Levy (similar preparation, but dissolved in ammonia) . .	2.5 " 6.0
Magnus-Levy (neutralized urine).	4.0 " 6.0
Simon (neutralized urine)	0.7 " 4.2
Simon (solution of isolated substance, precipitated with ammonium sulphate and dialyzed for eight weeks, neutral reaction) . . .	2.3 " 3.8
Fitz-Wright [precipitation with alcohol, solution in very dilute ammonia (Simon)]	1.7 " 3.6

Formation of "Albumosate." As regards the behavior of a solution of the substance on neutralization, after the previous addition of an acid

[1] Kühne and Chittenden. Loc. cit., vol. xx.

or an alkali, the reports of all observers who have examined in this direction, with the exception of Ribbink, are the same. Ribbink states that he could not obtain a precipitate on neutralization, but it is quite likely, as Magnus-Levy suggests, that he had previously not added enough acid or alkali. Kühne, who regarded the Bence Jones substance as an albumose, speaks of the apparent change which results on treating with an alkali, as due to the formation of an albumosate analogous to the albuminate in the case of the common albumins.

Behavior on Salting with Magnesium Sulphate. In its behavior toward magnesium sulphate a marked difference apparently exists between my substance and that of Magnus Levy. For, whereas he reports that on saturating the urine with the salt in question, at the temperature of the room, no precipitation occurred, I noted in my case that after acidifying with acetic acid the substance is promptly thrown down. My notes on this point read as follows: Upon the addition of two volumes and a half of a saturated solution of magnesium sulphate to the urine no precipitation occurred, even after acidifying with acetic acid, but on saturation of the acid solution with the salt in substance, complete precipitation occurred. Saturation without the addition of acetic acid gave no result in the native urine. But on treating the neutral solution of the isolated substance (precipitation with ammonium sulphate and subsequent dialysis for eight weeks) with two or three times its volume of a saturated solution of magnesium sulphate, and then saturating with the salt in substance, the Bence Jones body was completely precipitated on standing for twenty-four hours, at the temperature of the room. The filtrate remained clear on heating after the addition of acetic acid; no further precipitate occurred on treating with twice the volume of a saturated solution of ammonium sulphate, and the biuret reaction was negative. The precipitate itself was soluble in water and could hence not be a coagulate, but must be regarded as a true salt-precipitate. Other observers have made no notes of the behavior of the substance in this respect; but it is interesting to note that the substance which Dr. Wood sent me (from Fitz-Wright case) could also be precipitated with magnesium sulphate from its neutral aqueous solution.

Behavior on Digestion. On digestion with pepsin-hydrochloric acid all observers who have made investigations in this direction report that the substance dissolves very readily, and that the presence of "peptones" can very soon be demonstrated. Matthes noted that on prolonged digestion a jelly-like material separated out, which, after drying, was soluble in absolute alcohol. This, however, as he later admitted himself, and as Neumeister indicates, was owing to the admixture of a nucleo-albumin. Ellinger records that on digestion with pepsin for forty-eight hours a small amount of residue was obtained, which con-

tained phosphorus. In his case, however, a nucleo-albumin was also present and had not been previously removed. Speaking of the products of digestion with pepsin-hydrochloric acid, Kühne states that after one or two hours only "peptone" was found in solution, and no precipitate was obtained either with nitric acid or with acetic acid and sodium chloride.

A more detailed examination of the resulting products of digestion according to more modern methods has been made by Magnus-Levy. As I have previously indicated, he claims to have obtained a proto-albumose, three deutero-albumoses, and two peptones, while the formation of a hetero-albumose was not observed. In view of the importance of these results in their bearing on the question of the chemical nature of the Bence Jones substance, it may not be out of place to consider in some detail the basis on which Magnus-Levy has established his claim that on peptic digestion the Bence Jones substance yields a proto-albumose. Magnus-Levy states that he employed Hofmeister's method of analysis, as described by Pick,[1] Umber,[2] and Alexander.[3] According to this method the digestive mixture was neutralized (with ammonia or ammonium carbonate), brought to the boiling-point, and then concentrated on the water-bath to about one-fifth of the original volume. On neutralization Magnus-Levy states that he never obtained a precipitate, but that during the process of concentration flocculi separated out, which may have been due to acid albumin, but were present in too small a quantity for analytical purposes. On treating the filtered solution with an equal volume of a saturated solution of ammonium sulphate a precipitate then resulted, which Magnus-Levy regards as due to proto-albumose exclusively, as a hetero-albumose could not be obtained from this fraction, either on dialysis or on treating the aqueous solution of the precipitate with half and an equal volume of alcohol and boiling for several hours. He then further *identified* this fraction as proto-albumose by the following reactions, which he compares with those of the Bence Jones substance:

	Sulphur test.	Millon's reaction.	Biuret reaction.	Molisch's test.	Adamkiewicz test.	Salting with rock salt.	Rock salt and acetic acid.	Dilute copper sulphate solution.
1. Bence Jones substance	Markedly black color.	Intense.	Violet-red.	Faint but distinct.	Very pronounced.	No precipitation.	Complete precipitation.	Marked precipitation.
2. Proto-albumose	Markedly black color.	Markedly red.	Purely red.	Much more marked than under 1.	Faint.	Precipitation.	Precipitation more marked than with rock salt.	Marked precipitation.

[1] Loc. cit. [2] Loc. cit.

[3] F. Alexander. Zur Kenntniss d. Caseins u. seiner peptischen Spaltungsprodukte, Zeit. f. phys. Chem., 1898, vol. XXV. p. 411.

The limits of the precipitation were 3.2 and 4.8 in one test and 2.8 and 4.8 in a second.

The question which of course suggests itself on reading Magnus-Levy's paper is the following: Is it not possible that the proto-albumose, so called, was in reality a portion of the Bence Jones substance which had escaped digestion? I must confess that Magnus-Levy's account of his work is not sufficiently detailed as to render such a supposition unwarrantable. He states that after two to three hours, at the latest, the original substance had entirely disappeared, and that it was then already possible to demonstrate the presence of all the various fractions which he claims to have obtained. He does not state, however, in what manner he showed that the substance was no longer present, supposing that the substance had not been digested entirely. However, in that case it would certainly have remained in solution on neutralization and boiling, as the amount of acid previously added is scarcely sufficient to insure the precipitation of the substance on subsequent neutralization; and from the neutral solution the body would not have been precipitated on boiling. Even on acidifying again I have noted that the solution remains clear or becomes at best but slightly opalescent.

On the other hand, it might be argued that the behavior of the isolated proto-albumose, as compared with the Bence Jones substance, on salting with ammonium sulphate, as also in its general reactions, as tabulated above, would warrant the identification of the "proto-albumose" as a distinct substance. This I am willing to admit to a certain extent; but I have considered it necessary, nevertheless, to attempt to prove even more conclusively that the Bence Jones substance actually yields a proto-albumose on peptic digestion. To this end the experiments already detailed were undertaken, and the results show conclusively that a proto-albumose is actually formed, and my own work thus entirely confirms that of Magnus-Levy. A hetero-albumose is not formed. This was already suggested by Magnus-Levy's observation that on hydrolytic decomposition with hydrochloric acid and sulphuric acid the Bence Jones substance does not yield glycocoll, but furnishes a relatively large amount of tyrosin, with but little leucin.

As regards the remaining products of peptic digestion which may be obtained from the Bence Jones substance, I also have found bodies corresponding to Pick's deutero-albumoses A, B, and C. A and C, however, and notably the latter, were manifestly only produced in very small amounts, while B was present in fairly large quantity. Peptone A also was certainly only present in traces, if at all, while I could demonstrate a considerable amount of peptone B. Magnus-Levy states that his deutero-albumose B showed a minimal Molisch reaction; I obtained none whatever. However, Magnus-Levy himself has placed a sign of interrogation behind his (minimal).

Chemical Nature of the Bence Jones Substance. Regarding the chemical nature of the Bence Jones substance, it is clear from the foregoing considerations that neither Magnus-Levy nor I regard the body as an albumose, and I note that Rostoski also has come to this conclusion, though he does not cite any experiments as basis for his belief.

Kühne regarded the insoluble (in neutral saline solution), coagulated substance as dysalbumose, and supposed this to have resulted from hetero-albumose, in which form the body must have been present in the urine in solution. In addition, he suggests that deutero-albumose and proto-albumose may also have been present in traces, so that, according to Kühne, the Bence Jones substance represented a mixture of several albumoses. Huppert likewise regards his body as a hetero-albumose, especially as the substance is rendered insoluble by salting to saturation with sodium chloride at 35° C. to 40° C. The remaining observers, with the exception of Magnus-Levy, Rostoski, and myself, also regarded the substance as an albumose, while admitting, however, that it does not coincide in its reactions with any one of the known digestive albumoses. The essential points of difference are given by Matthes as follows:

1. If much salt is present the coagulated substance is not *entirely* soluble on boiling, while a precipitated albumose is soluble at 100° C. no matter how much salt may be present.

2. An aqueous solution of the substance does not pass through animal membrane, even in traces, while both proto-albumose and deutero-albumose are dialyzable to some extent.

3. The substance in question after coagulation is still soluble on washing with distilled water, as also on dialysis, especially if this is continued until practically all salt has been removed. Hetero-albumose, on the other hand, is entirely insoluble in distilled water, and is precipitated on dialysis.

4. The substance differs from hetero-albumose in the fact that it is apparently coagulated by heat, in any concentration, in the presence of a small amount of salt and acid, while hetero-albumose only coagulates in very concentrated solutions.

In addition to these factors the following also can be urged against the albumose nature of the substance, and especially against the assumption that the body may be a hetero-albumose:

1. The fact that the solubility of the coagulated substance at 100° C. may be changed at will, and that under certain conditions the coagulate is altogether insoluble at 100° C., even though the reaction of the urine and its chemical composition have not been altered by artificial means.

2. The fact that after precipitation with alcohol or with salt and acid

at ordinary temperatures the substance rapidly becomes insoluble in distilled water and neutral saline solutions. In this respect hetero-albumose resembles the Bence Jones substance, but it is to be noted that this change cannot be effected by heat.

3. The apparent formation of syntonin and alkaline albuminate on treating with acids and alkalies. In this respect the substance resembles the true albumins, but the precipitates which result on neutralization are not altogether insoluble, as in the case of the common coagulable albumins.

4. The Bence Jones substance contains a carbohydrate group, which is lacking in the hetero-albumose—of fibrin, at least.

5. Hetero-albumose (of fibrin) contains 17.98 per cent. of nitrogen, of which 39 per cent. exists as diamino-nitrogen; whereas the Bence Jones substance contains 15.57 per cent. of nitrogen, of which 25 per cent. are referable to diamino-nitrogen.

6. On hydrolytic decomposition hetero-albumose yields glycocoll and but little tyrosin, while from the Bence Jones substance no glycocoll can be obtained, but relatively much tyrosin.

7. On peptic digestion the Bence Jones substance yields a proto-albumose, showing that its molecule must be more complex than that of the primary albumoses.

We are thus forced to the conclusion that the substance cannot be an albumose; but in attempting to classify it among the remaining groups of proteins we meet with further difficulties. The fact that many observers have found phosphorus in the mineral ash would at once suggest that the substance might be a nucleo-albumin, but opposed to this assumption is the statement of Magnus-Levy that by previously removing the phosphates from the urine with ammoniacal magnesia mixture he was able to obtain specimens which were entirely free from phosphorus. None of the previous observers, moreover, has succeeded in demonstrating the separation of a nuclein, on peptic digestion, if care had been taken to eliminate the presence of a contaminating nucleo-albumin. Matthes, who originally regarded his substance as a nucleo-albumose, later abandoned this idea, and concluded himself that the jelly-like material which separated out on prolonged peptic digestion was referable to the admixture of a nucleo-albumin with which the Bence Jones substance had nothing to do. In Dr. Wood's case, moreover, I also succeeded in finally obtaining a product which was free from phosphorus.

In the solubility of the alcohol precipitate in dilute ammonia the substance resembles the histons, but it differs from these in the fact that the body cannot be precipitated by ammonia from its acid solutions.

The solubility of the alcohol precipitate in dilute ammonia further distinguishes the substance from the true coagulable albumins which

have thus far been studied. Those, moreover, which ordinarily appear in the urine are totally insoluble at 100° C. unless the chemical composition of the urine is artificially altered, as by the addition of excessive amounts of urea, etc. Magnus-Levy has pointed out that, like casein, the Bence Jones substance lacks the hetero group, but it differs from it in the absence of phosphorus and the presence of a carbohydrate group. As his substance was not precipitated by salting with magnesium sulphate, or on passing a current of carbon dioxide through its solution, and as it proved soluble in distilled water, he concludes that the body does not belong to the class of globulins, even though in his case the limits of precipitation of the deutero-albumose A were the same as those of the corresponding deutero-albumose obtained from serum globulin. This relation and the limits of precipitation of the various other digestive products of the Bence Jones substance as compared with those of the more common albumins is shown in the accompanying table:

	Fibrin.	Egg albumin.	Serum albumin.	Serum globulin.	Bence Jones albumin.
I. Primary albumoses . . .	2.6—4.4	3.6—4.6	4.2—4.6	3.6—4.6	2.8(3.2)—4.8
II. Deutero-albumoses:					
Deutero-albumose A . .	5.4—6.2	5.6—6.0	5.4—6.2	5.6—7.2	5.6—7.2
Deutero-albumose B . .	7.2—9.5	7.0—7.8	7.2—8.0	7.8—8.6	7.8—9.2

In contradistinction to Magnus-Levy's observation, I found that my substance could be precipitated by salting with magnesium sulphate to saturation, while at the same time there was no evidence whatever that the urine contained any other albuminous body in solution but the Bence Jones substance. Other observers, as I have already stated, failed to make a note of the behavior of the body in this respect, but with the material which Dr. Wood sent me from the Fitz-Wright case No. 2 I obtained the same result.

Why my results should differ so radically in this respect from those of Magnus-Levy I am unable to say, unless, indeed, his solutions were not altogether saturated. To insure this point I followed the suggestion of Marcus,[1] and treated the solution with from two to three times its volume of a saturated solution of magnesium sulphate, and then added the salt to saturation (Marcus, p. 567). The observation, however, is important, as it suggests that the Bence Jones substance may at least be closely related to the globulins, if, indeed, it is not a globulin itself. The fact that it is soluble in water cannot be adduced as an argument to the contrary, since it has been conclusively established that even in

[1] E. Marcus. Ueber in Wasser lösliches Serumglobulin, Zeitsch. f. physiol. Chem., 1899, vol. xxviii. p. 559.

normal blood a serum-globulin exists which is water-soluble. According to Marcus, indeed, that portion which is insoluble in water represents but 9 to 23 per cent. of the entire quantity that may be precipitated by magnesium sulphate. This water-soluble portion, as would be expected, is not precipitated by dialysis. The substance gives the xanthoproteic reaction, the sulphur and biuret reactions, that of Adamkiewicz, as also that of Molisch. An estimation of the nitrogen gave 15.9 per cent.—*i. e.*, a figure which approximates that which has been found for the Bence Jones substance, viz., 15.56 to 15.59. It is noteworthy, moreover, that in the case of a pure solution of the substance not even a turbidity is produced by means of a current of carbon dioxide, so that this point also cannot be brought forward as an argument that the Bence Jones substance should not be viewed as a globulin. On the contrary, I believe I have shown that cogent reasons exist for the assumption that the body is indeed closely related to the water-soluble globulin, as Marcus describes it. My material, however, was unfortunately not sufficient to institute a more detailed comparison between the two substances; and for other reasons also it seemed advisable to publish my results so far as they go.

Should further research bear out the correctness of my view, the previously supposed identity of Noël Paton's[1] crystalline globulin with the Bence Jones substance would appear to be rendered quite probable. Huppert,[2] indeed, had previously attempted to prove their identity and at one time regarded Noël Paton's substance as an albumose; later, however, he abandoned this view,[3] and at present I think there can be no doubt that this substance also was in reality a globulin. In many respects the description of the body reminds one strongly of the Bence Jones substance. As in Bence Jones' case, it was eliminated in enormous quantities (15.0 to 70.0 pro mille, corresponding on one occasion to an elimination of 70 grammes in twenty-four hours), and, barring the Bence Jones substance, it is, indeed, the only albuminous substance which has ever been encountered in the urine in such large amounts. In this case, also, no tube-casts were found in the urine, and post-mortem examination revealed the absence of a nephritis. A further point of resemblance is the fact that Paton's globulin was obtained in crystalline form, and was deposited as such spontaneously from the urine. This occurred at times on standing for only one or two days;

[1] Byrom-Bramwell and D. Noël Paton. On a Crystalline Globulin Occurring in Human Urine, Reports from the Laboratory of the Royal College of Physicians, Edinburgh, 1892, vol. iv. p. 47.

[2] Huppert. Ueber einen Fall von Albumosurie, Zeitsch. f. physiol. Chem., 1896-1897, vol. xxii. p. 500.

[3] Huppert. Ueber den Noël Paton'schen Eiweisskörper, Centralbl. f. med. Wissen., 1898, p. 481; cit. in Maly's Jahresber., 1899, vol. xxviii. p. 302.

at other times only after weeks or months. A solution of the crystals in neutral saline solution coagulated between 56° C. and 59° C. Very suggestive also is the following observation, which is recorded in Huppert's second communication: "The coagulum dissolves in warm water after the addition of a few drops of a sodium carbonate solution, and on neutralization with hydrochloric acid a flocculent precipitate is formed, which apparently did not dissolve upon the addition of 5 per cent. of rock salt; but on heating the filtrate a turbidity occurred at 52° C." On boiling it is stated that the urine coagulated almost in bulk, and it would thus appear that Paton's substance differed from that of Bence Jones'; but, as I have shown, the behavior on boiling cannot be regarded as a criterion in differentiating between the latter and the common coagulable albumins. In other respects, it is true, points of difference apparently exist between the two bodies; but, on the whole, these are unimportant, and I believe that we may very well classify the two together. Although future researches may show that they are not identical, there is evidence to prove even now that they are at least closely related.

The case occurred in Byrom-Bramwell's practice, while the urinary examination was conducted by Noël Paton. Evidence of bone disease did not exist during life, but it is unfortunate that post-mortem a more detailed examination could not have been made.

The Origin of the Bence Jones Substance. Of the seat of origin of the Bence Jones substance very little is known that is definite. Ellinger states that he found a substance in the blood of his patient which gave the common albumose reactions and coagulated at about the temperature of the isolated body (he indicates 38° C. to 40° C.!). Ribbink and Askanazy, on the other hand, who are the only observers who made investigations in this special direction, report negative results. Ellinger does not state whether the blood in his case was withdrawn during the life of the patient, but even if this were done the result can scarcely be surprising unless, indeed, the substance was formed in the kidneys—a supposition for which there is no tangible basis.

Askanazy states that he did not find the substance in the tumor masses, but found it in a fresh extract of the bone-marrow, which, however, was the seat of extensive lymphadenoid degeneration. Ribbink, on the other hand, records that in his case it was present neither in the bone-marrow nor in the bone-substance. Ellinger reports similar findings in the case of the tumor masses, as of the blood, and Dr. Wood writes me that he obtained the same substance, which was present in the urine, from the diseased portion of the bone tissue, and that he did not find it in the bone-marrow in any other portion of the body of

Wright's patient. Other observations on this point do not exist, but it seems to me that the findings of Ellinger and Wood more especially are very suggestive.

Most observers have been of the opinion that the Bence Jones substance originates in the diseased bone-marrow, and I must confess that Magnus-Levy's arguments to the contrary are but little convincing. He thinks that the amount of the albumin that may appear in the urine is too large to have originated in the small tumor masses. He argues as follows: "The entire amount of bone-marrow of the ribs does not exceed 200 grammes (calculated according to Dursy and Friederich in Vierordt's tables), with about one-fifth—*i. e.*, 40 grammes—of albumin. Only a portion of the marrow is replaced by myelomata. There are in addition, to be sure, the tumor masses, which may occur in other portions of the skeleton, but the combined weight of these is only very rarely notable (more than 500 grammes, corresponding to 100 grammes of albumin)—at least not in the earlier stages of the disease; and at this time the elimination of the substance, in my case, at least, reached its greatest height. It seems altogether excluded that in (relatively) such small tumor masses from 36 to 70 grammes of an abnormal albumin should daily be formed, viz., an amount which probably exceeds the weight of the dried masses themselves." Such an assumption seems to me unwarrantable, for we may readily imagine that the Bence Jones substance could result from the common albumins of the blood—such as serum globulin, for example—through enzymatic activity referable in myeloma, at least, to the plasma cells of the bone-marrow.

It would be exceedingly interesting to ascertain in a future case where such a very large elimination of the substance may again be noted as in Bence Jones' and Magnus-Levy's cases, whether the normal globulins of the plasma are present, if at all, in normal amount. Supposing that the Bence Jones substance were actually produced in the manner indicated, it might be argued that as the plasma cells are normal components of the red marrow, traces, at least, of a corresponding body should even normally be demonstrable in the urine, which does not occur. But while accepting Wright's conclusion that the neoplasm, exclusive of its vessels and insignificant stroma, may have arisen from an abnormal proliferation of the plasma cells of the red marrow, it seems reasonable, I think, to assume that with the abnormal proliferation of the cells there is associated some deviation from their physiological function, of which, in turn, the appearance of the Bence Jones substance is the expression. According to this supposition, the body in question would appear in the urine, for the reason that it is foreign to the body, and we should accordingly also expect that following its

artificial introduction into the blood current it would reappear in the urine. In the human being such experiments have, for obvious reasons, not been made, and it may be questionable whether the results of corresponding experiments in the case of animals can be directly adduced as evidence in the question under consideration. However, so far as they go they support the hypothesis that has been propounded. Kühne thus states that he sent a specimen of his material to Stokvis, and that the latter found the substance in the urine after intravenous injection as also following its introduction into the rectum.[1] Matthes also states that following the subcutaneous injection of the substance in dogs it reappears in the urine. Ellinger, on the other hand, reports that the intravenous injection even of large quantities (5 grammes in 75 c.c. of sodium carbonate solution injected into a dog weighing 6 killogrammes within two minutes) did not lead to the appearance in the urine of a substance that could be precipitated by salting with ammonium sulphate to saturation; but he adds that the filtrate of the salted urine gave a strong biuret reaction, which suggests that a substance or substances were present which were identical with or closely related to true peptone (in the sense of Kühne), and which may possibly have been derived from the injected material.

For the possible assumption that the Bence Jones substance originates during the process of gastric or intestinal digestion there is at present no basis.

NOTE.—Since writing the above an additional case of Bence Jones albuminuria (the twenty-third) has been observed in the service of Hijmans van den Bergh, in Rotterdam. An account of the clinical history and the post-mortem findings has not as yet appeared, but a detailed study of the patient's urine has been published by A. Gutterink and C. J. de Graff ("Ueber d. Darstellung einer krystallinischen Harnalbumose," *Zeit. f. Phys. Chem.*, 1902, vol. xxxiv. p. 392). Of special interest is the observation that the writers succeeded in crystallizing the albumin at will. A more detailed study of the chemical nature of the body is in progress.

[1] Kühne. Ueber Hemialbumose im Harn, loc. cit., p. 214; and Stokvis, Maandblad voor Naturwetenschappen, 1872, No. 6.

PARATYPHOID INFECTIONS:[1]

WITH REPORT OF A CASE CLINICALLY IDENTICAL WITH TYPHOID FEVER IN WHOSE BLOOD A PARATYPHOID BACILLUS WAS FOUND.

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Since Gärtner's discovery of the B. enteritidis, in 1888, increasing interest has attended the study of the intermediate members of the typhoid-colon group of bacilli. In 1893 Gilbert proposed the terms "paratyphoid" and "paracolon" to designate these intermediates; but Durham regards the terms as inappropriate, since he believes that the intermediates are well-defined species of organisms, and suggests that all be classified under the group name "Gärtner and its allies." From the clinical stand-point, however, the term paratyphoid is the most clearly descriptive that can be applied to infections resembling typhoid and caused by one of these intermediate bacilli.

According to Durham, the Gärtner group includes B. enteritidis and the similar organisms described in association with epidemics of meat-poisoning, the gas-producing "typhoid" bacilli which have been described by various observers, the B. psittacosis, the paracolon bacillus described by Gwyn, and the bacillus O (Cushing). Theobald Smith has shown that B. choleræ suis and B. typhi murium should be classified with this group, and Cushing suggests that the recent researches of Reed and Carroll on the B. icteroides of Sanarelli demonstrated that it, too, belongs here. In addition, Widal adds the bacillus of calf septicæmia of Thomassen.

Pathogenicity in the human subject has been established for certain members of the Gärtner group—*e. g.*, B. enteritidis in epidemics of meat-poisoning, B. psittacosis in a peculiar epidemic bronchopneumonia with typhoid symptoms in some cases, and the paratyphoid bacilli in cases resembling typhoid fever. Moreover, Grünbaum has suggested that febrile jaundice may be caused by one of the intermediates, since he has obtained the Widal reaction with sera from these cases.

Petruschky's bacillus fæcalis alkaligenus, according to Durham's latest work, is not an intermediate of the typhoid-colon group, but occupies

[1] Read at a meeting of the New York Pathological Society, February 12, 1902.

a place beyond the typhoid in that it does not acidify any sugar-containing media; in a sense it out-typhoids the typhoid bacillus.

In the present paper we shall concern ourselves chiefly with cases clinically resembling or identical with typhoid fever which were apparently caused by an intermediate bacillus.

In 1896 Achard and Bensaude reported two cases which they considered due to infection with paratyphoid bacilli.

Case I.—Woman, aged twenty-four years. Had never had typhoid fever. For several weeks had nursed a child ill with a "mucous fever." Taken sick August 24th with a chill, followed by fever, anorexia, slight diarrhœa, marked prostation, and tympanites. No spleen, no epistaxis, no rose-spots. Temperature, 103.3° F. No râles in the chest. Intestinal hemorrhage. September 11th, marked pyuria. September 14th, temperature fell suddenly to 98.6° F. without apparent cause, remounting to 100.4° F. September 20th, temperature 98.6° F., rising to 102.2° F. on the 23d, with a return of the diarrhœa and the development of right femoral thrombosis. October 2, left femoral thrombosis. October 5th, temperature normal.

Blood from vein at elbow remained sterile. Urine taken aseptically September 12th and 23d, both times gave a bacillus which was considered to be a paratyphoid. Blood aspirated from the spleen showed staphylococci, but no bacilli. Stools gave colon only.

September 9th, no Widal. September 14th, the serum reaction with same typhoid culture and the bacillus obtained from the patient's urine was positive. September 17th, two cultures of typhoid bacilli gave the reaction. October 16th, positive Widal with three of thirteen cultures of typhoid bacilli. Reaction constantly positive with paratyphoid. Constantly negative with colon. Seven weeks after the fever the patient's serum agglutinated the bacillus obtained from the urine and two cultures of paratyphoid bacilli, but was without action on five cultures of typhoid. The blood of animals immunized with the bacillus from the urine reacted with paratyphoid bacilli, and only with certain samples of typhoid bacilli.

The authors think the case presented a close analogy to typhoid fever complicated by pyelonephritis, with a relapse complicated by femoral thrombosis.

Case II.—Infant, aged seven months. June 23d, temperature was 100.4° F., with subcrepitant râles over middle of left lung posteriorly. Temperature reached 104° F. on the 26th. The pulmonary signs disappeared, but the fever continued between 102.2° F. and 104° F. Tympanites, rose-spots in abundance. July 13th, temperature 98.6° F. Discovered swelling of right sterno-clavicular articulation, which was opened and a paratyphoid bacillus recovered from the pus. Patient recovered completely.

The authors conclude that while general infection with B. typhosus cannot be excluded in this case they can affirm positively that the local infection was paratyphoid in nature.

In discussing the paper, Rendu states that the authors have demonstrated that paratyphoid fever closely resembles typhoid in its course,

temperature curve, and abdominal symptoms. Cases of psittacosis infection, he says, may present the general appearance of typhoid fever, but show special pulmonary localization. He has seen three cases. All three presented signs of grave bronchopneumonia. None had diarrhœa, rose-spots, or tympanites. One died. There were no intestinal lesions at the autopsy.

In the following year, in his thesis, Bensaude contended that the bacilli isolated from these cases were B. psittacosis not paratyphoid as originally reported, but his bacteriological evidence only proves that the bacilli were intermediates. He did not conclusively differentiate the bacillus of psittacosis from paratyphoid bacilli. Moreover, he seems in doubt as to the real nature of the general infection in the two cases.

In 1897 Widal reported the following case: A tubercular patient, after three weeks in the ward, developed an abscess in the neck about the œsophagus, presenting at the same time slight constitutional symptoms. A bacillus was obtained from the pus, which, from its cultural characteristics, Widal considered a paracolon. The bacillus gave a marked reaction with the serum of the patient in dilutions as high as 1 : 1000, the reaction steadily diminishing with convalescence. Widal concludes that the bacillus isolated was the cause of the patient's infection. The sera of animals inoculated with B. coli communis and with B. psittacosis gave no reaction with this organism.

Gwyn isolated, in 1898, from the blood of a patient suffering with a disease clinically identical with typhoid fever a bacillus which culturally corresponds with Widal's. The patient had been ill since September 17th, with headache, fever, weakness, and later with vomiting, diarrhœa, and pain in the abdomen. October 16th he had three hemorrhages from the bowel. He slowly rallied and went out of the hospital in five weeks. Rose-spots were present, the spleen was palpable, the urine gave the diazo-reaction. The temperature was that of a severe typhoid. The Widal reaction was never found. Blood cultures taken October 12th gave a paracolon bacillus. The patient's serum reacted with this bacillus in dilutions of 1 : 150 to 1 : 200. Two months after the date of the culture there still remained a slight reaction. The same serum was without action on B. typhosus in any dilution above 1 : 1 to 1 : 5.

Cushing's case followed in August, 1900. M. B., colored, aged twenty-seven years. From early in June, 1898, nine months before admission, the patient had suffered with a prolonged course of fever extending over a period of ten weeks. Clinically, it was typhoid fever, with a severe but typical course. There was a relapse ushered in by profuse epistaxis. During convalescence two tender swellings developed near the breast-bone. One disappeared, the other burst, dis-

charging a large amount of pus and leaving a sinus at the level of the fifth rib. Microscopical examination showed the process to be an osteomyelitis. There was no Widal reaction. Cultures taken from the sinus at the time of the operation gave an intermediate bacillus, which Cushing calls bacillus O.

In the same month appeared Schottmueller's first case. Male, aged twenty-six years. The patient was taken ill July 23d with headache and catarrh of the upper respiratory passages. Temperature 104° F. July 27th, the patient was sleepy and tired; spleen palpable. July 28th, the sixth day of the disease, the blood furnished a bacillus resembling the typhoid, but fermenting glucose. Rose-spots present. Temperature normal, August 5th. The only symptom of typhoid lacking was the stools. August 1st the Widal reaction was negative, while the bacillus isolated from the blood reacted with the patient's serum at 1 : 50, but not in 1 : 100. Later the reaction was obtained at 1 : 100. With three other typhoid cultures the reaction was negative. Of the sera of four typhoid patients only one gave a reaction with the bacillus, and that at 1 : 20.

In 1901, Schottmueller reported five more cases, clinically like typhoid fever, in whose blood he found paratyphoid bacilli. None of the cases gave the Widal reaction. There was a sixth case which did not give the Widal reaction from whose blood he failed to obtain a bacillus, but this may be explained by the fact that the blood was drawn only three days before the end of the fever.[1]

Case I.—Male, aged sixty years. Taken ill July 7th with headache, lassitude, diarrhœa. Spleen not palpable. No spots. Temperature, 104° F. Temperature normal August 1st. Mild type.

Case II.—Male, aged eighteen years. Taken ill July 13th with headache, etc. Temperature 105.2° F. July 18th, condition bad. July 28th, condition dangerous. September 18th, discharged cured. Severe typhoid type.

Case III.—Male, aged nineteen years. Taken ill August 16th with headache, etc. Temperature, 104.3° F. Rose-spots present. October 1st discharged cured. Very mild type.

Case IV.—Male, aged forty-six years. Taken ill about August 12th with headache, etc. Had been in bed six days before admission to hospital. Rose-spots present. Spleen palpable. Temperature 103° F. Discharged cured December 14th. Mild type.

Case V.—Male, aged fifteen years. Admitted November 3d. For fourteen days had been ill with fever, lassitude, etc. Temperature 105.4° F. Many rose-spots, which appeared on the face and hands as well as in the usual situations. Patient in bad condition until November 12th. December 30th he was discharged cured. Severe typhoid.

Case VI.—Male, aged twenty-five years. The patient was a physi-

[1] In a limited number of cases of typhoid fever we have failed to find the bacillus in the blood after the second week, and it will be noted in our case of paratyphoid infection that the blood drawn on the twenty-seventh day of the disease remained sterile.

cian who had assisted in the examination of Case II. Temperature 101.6° F. Dismissed cured September 16th. The blood did not give the Widal reaction. Blood taken three days before the end of the disease remained sterile. The diagnosis of typhoid fever was made by exclusion.

There were no complications with any of the cases, even the severe ones. Case IV. was alcoholic, Case I. was sixty years of age. In these cases, the author says, one would expect a bad prognosis in true typhoid fever, yet both were mild.

The six cases above recorded occurred in a series of sixty-eight cases which Schottmueller examined, a high proportion, if we can judge by the comparative frequency of the Widal reaction in typhoid fever.

Schottmueller applies the term paratyphoid both to the infection and to the bacillus.

Kurth also published, in 1901, five cases which he considered paratyphoid fever. These cases were found among sixty-two whose sera were tested for the Widal reaction.

CASE I.—Woman, aged thirty years. Taken sick May 17th. Temperature 103.2° F. Normal June 11th. Tendency to constipation. Widal negative except in dilution of 1 : 3. June 30th the bacillus was recovered from the urine.

CASE II.—Male, aged twenty-nine years. Taken sick August 27th, having had headache for a week, with fever and diarrhœa. Splenic tumor, rose-spots, diazo-reaction. Temperature 100.4° F. to 104.9° F. No complications. Widal negative three times. Bacillus isolated from stools September 19th. The patient's serum reacted with this bacillus at 1 : 8000, and on October 28th at 1 : 2000.

CASE III.—Male, aged twenty-five years. Taken sick September 3d with headache and vomiting. Splenic tumor, few rose-spots, diazo-reaction. Temperature up to 104° F. Widal reaction was tested three times, and was positive once at 1 : 3. No paratyphoid bacilli found either in stool or in urine. The patient's serum reacted with the bacillus from Case II. at 1 : 500.

CASE IV.—Male, aged eighteen years. Taken sick October 26th. Typhoid stools. Temperature 98.6° F. to 104° F. Normal November 27th. Rose-spots, splenic tumor. Widal negative twice. The patient's serum reacted with the bacilli from Cases I. and II. at 1 : 500.

CASE V.—Woman, aged twenty-three years. Entered hospital November 7th. No splenic tumor; doubtful rose-spots; no diazo-reaction. Irregular temperature, never above 102.2° F. Serum reaction positive.

All the cases were mild. None had complications. In Cases III. and IV. the cultures were not taken till late in the disease, which may explain the negative result.

In the course of a study on the bacteriology of the blood in typhoid fever we encountered the following case:

Louise R., colored, aged twenty-eight years, entered Bellevue Hospital in the service of Dr. Loomis, October 9, 1901. She gave the

following history: For the last two months she had been living in Elizabeth City, N. C., and was taken ill one week after her return to New York. On October 4th the patient had a chill which lasted about half an hour and was followed by fever and sweating. Her appetite has been poor and she has had frequent attacks of vomiting, the vomitus consisting of the food last eaten. There have been two attacks of epistaxis. Since October 6th she has suffered from severe headache. Her bowels have moved freely, with a slight tendency to diarrhœa. The patient feels very weak. Temperature on admission was 103.2° F., pulse 92.

Physical examination on admission. The patient is well nourished, the muscles are firm, the skin is moist and elastic. The mucous membranes are red. The tongue is tremulous, fissured, coated over the dorsum, red at the tip and edges. The pulse is small, frequent, regular, and of low tension. The heart is negative. The lungs are negative except for slight impairment of resonance posteriorly. The abdomen is soft, but gives a tympanitic note. Liver normal. Spleen not palpable. Slight epigastric tenderness. Owing to the patient's color we could not determine the presence of rose-spots.

The patient had two stools on each of the first two days in the hospital, but had been given a dose of castor oil. Subsequently there was slight constipation.

An examination of the urine, made October 10th, showed a trace of albumin, with granular and hyaline casts, blood, pus, and epithelial cells. A leucocytic count October 11th gave 10,600. The same day the blood was examined for the malarial parasite, with a negative result. The Widal reaction, tested by Dr. T. W. Hastings, was tried three times: October 10th, dilution 1 : 80, negative after one hour; October 16th, dilution 1 : 40, negative after half an hour; October 31st, dilution 1 : 80, negative after one hour. With another culture of typhoid bacilli an imperfect and only partial reaction was obtained at the end of an hour in a dilution of 1 : 20. On October 9th, the sixth day of the disease, and on October 30th, the twenty-seventh day of the disease, 10 c.c. each of blood were taken from a vein at the elbow for bacteriological examination. The first of these specimens gave a paratyphoid bacillus, the second remained sterile.

Clinically the patient followed the course of a mild attack of typhoid fever. The spleen became palpable as the disease progressed. The subsequent history was uneventful except for a sharp break in the temperature to 99.6° F. on the fourteenth day of the disease, after which the exacerbations and remissions were very marked till the twenty-second day, when the temperature fell to 98.6° F. and convalescence was definitely established. The patient was discharged cured November 20th, six weeks after entrance to the hospital and seven weeks after the beginning of her illness.

Rose-spots were sought for many times, but because of the patient's color it was impossible to decide if they were present.

To sum up: The illness was ushered in with a chill, followed by fever, anorexia, lassitude, slight diarrhœa and fibrillary tremor of the tongue. The temperature curve was continuously high to the fourteenth day of the disease, when it fell to 99.6° F., after which the curve was broken by exacerbations and remissions to the twenty-second day,

the first day of convalescence. Added to these symptoms there was splenic tumor. So that in all essential features the case was typical of mild typhoid fever.

Analysis of the Symptoms of Paratyphoid Fever. In view of the care with which the cases from whose blood the paratyphoid bacilli have been isolated were studied, it must be admitted that these organisms are capable of causing a general infection that has to be reckoned with in the diagnosis of typhoid fever. An analysis of the symptoms of the reported cases demonstrates that this infection closely resembles true typhoid infection, and may even be identical with it in clinical manifestations. Practically all of the cases of paratyphoid infection passed clinically for typhoid fever, without a Widal reaction, until careful bacteriological examination revealed their true nature.

In so far as conclusions can be drawn from the limited number of cases reported, paratyphoid infections may be mild or severe as in genuine typhoid. The symptoms of invasion are practically the same, for we may find in both headache, lassitude, anorexia, diarrhœa, epistaxis, chill followed by fever, and slight inflammation of the upper respiratory passages.

Moreover, during the course of paratyphoid infection the patient develops the typhoid state, slight or profound, accompanied by tympanites, diarrhœa or constipation, rose-spots, splenic tumor, and quite a typical temperature curve. The pulse is that of typhoid fever. The urine sometimes gives the diazo-reaction.

Abscess of the neck, osteomyelitis, pyelonephritis (?), and intestinal hemorrhages have been reported as complications. Even a relapse occurred in Cushing's case. So that the picture is more or less complete as a whole.

For the most part the cases have been mild, and Schottmueller states on the evidence of his seven cases that the prognosis is favorable.

Certain irregular typhoid cases have been reported in which the Widal reaction was absent, which we are inclined to regard as examples of paratyphoid infection. Brill has made a careful study of seventeen of these cases. In our case there was a remarkable break in the temperature curve, without assignable cause, to 99.6° F. on the fourteenth day of the disease, though the temperature afterward remounted to 101.8° F. Possibly some of the cases of the so-called fourteen-day type of typhoid fever are really paratyphoid fever, but we have been unable to obtain any data on this point. Dr. Thomas D. Coleman, of Augusta, Georgia, writes us that the fourteen-day typhoid fever is quite common in that section, and that in all essential symptoms it is identical with the twenty-one-day type. He also states that the Widal reaction was negative in one of these cases, but a bacteriological examination of the blood or feces was not made.

Brill's cases bore a marked clinical resemblance to typhoid fever, though the duration of the disease was only ten to twelve days. The serum reaction of these cases was tested with typhoid bacilli daily, with negative results. The symptoms, briefly stated, were: anorexia, malaise, headache, and general body pains for three or four days, succeeded by rigors or a chill, and sometimes epistaxis. The temperature rose rapidly to 104° F. to 105° F., after which a mild typhoid state developed. Rose-spots were generally present. The spleen was enlarged. Constipation was the rule. The temperature reached normal ten or twelve days after the beginning of the illness. Inconstant diazo-reaction. No leucocytosis. No intestinal hemorrhage. No complications or sequelæ.

In three of the cases cultures were made from the feces and B. coli communis obtained. In one case the spleen was aspirated, and again B. coli communis found. The serum of each case was tested for a reaction with the colon bacillus and found negative. And in two cases the serum of the patients was tested with colon bacilli obtained from themselves, with no reaction. In these two cases then the bacilli could not have been paratyphoid bacilli.

Case XIV. of Brill's series is especially remarkable. The patient had had typhoid fever, with the Widal reaction, six months previously and had entirely recovered. The serum reaction against the typhoid bacillus persisted up to and including part of the second illness, during the course of which it disappeared. Brill justly claims that the second attack was not typhoid fever.

The cases reported as fatal typhoid fever with intestinal lesions, not showing the Widal reaction, without bacteriological examination are not proved to have been genuine typhoid infection.

The Widal Reaction in the Light of Infections by Members of the Gärtner Group of Bacilli. Since the introduction of the serum reaction as a means of diagnosis in typhoid fever it has been a well-recognized fact that a small proportion of cases which are clinically typhoid fever fail to give the reaction. Brill, adding to Cabot's statistics, finds that of 4879 cases 4781, or 97.9 per cent., gave the reaction. Gwyn gives 99.6 as the percentage of positive reactions in the Johns Hopkins Hospital. On the contrary, in all the reported cases of paratyphoid infection the reaction has been absent. It is probable, then, that some, at least of the typhoid cases with negative reaction, were really paratyphoid. That not all of them were paratyphoid is made probable by the following remarkable case reported by H. Batty Shaw:

Adult. Headache for three days. Temperature 103° F. Typhoid fever was suspected, and on the two following days the Widal reaction was tried at 1 : 50, and both times failed. On the seventh day of the disease rose-spots appeared and remained visible until the nineteenth

day. Splenic tumor. Delirium and incontinence for three weeks. Temperature normal the twenty-fourth day. An abscess developed in the region of the right rectus abdominis. It was incised the thirty-sixth day of the disease and a typhoid bacillus isolated from the pus. The patient's own serum in dilution of 1 : 200 failed entirely to clump this bacillus after an hour's exposure. Another typhoid case in the hospital, giving the Widal reaction with another typhoid culture, failed to react with this bacillus at the same dilution. The serum of the patient was then tried with a typhoid culture from University College, but in dilution of 1 : 100 gave only the slightest clumping after twenty-four hours. The same culture with the serum of another patient with typhoid fever gave the reaction in two minutes.

The bacillus isolated corresponded to the following biological and other tests: 1. Decolorized by Gram. 2. Actively motile in broth—no scum. 3. Shake preparation in glucose-agar, no gas. 4. No indol in broth after ninety-six hours. 5. Growth on potato present, but not visible. 6. Did not curdle milk.

No adequate explanation offers itself in this case, except some biological peculiarity which was not demonstrated. It scarcely seems possible that the bacillus isolated was not the cause of the patient's infection.

It cannot be assumed that all cases, clinically typhoid, which have been reported as giving the Widal reaction were cases of genuine typhoid infection. The brilliant work of Durham on the typhoid colon group and their serum reactions has established the fact that certain members of this group may be mutually interacted upon by sera of infected patients and immunized animals. This is especially true of sera in low dilution, and since in the earlier years of the Widal reaction the technique had not been worked out, and dilutions were more frequently low than not, some of the cases reported as typhoid fever may have been paratyphoid. The simple fact that clumping of bacilli has been obtained is not sufficient evidence for diagnosis. Gruber and Durham have proved that a serum reaction is not in the strict sense *specific*, that it is only a *special* reaction, and that it indicates not a certainty, but a probability.

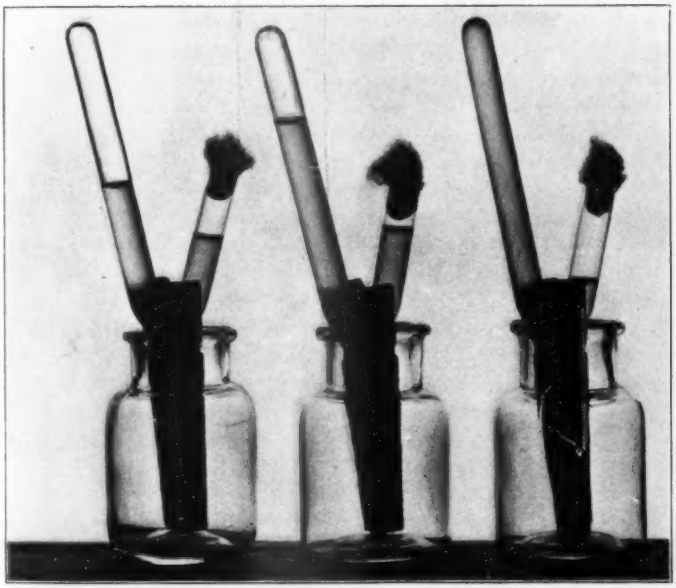
Landsteiner was the first to observe that typhoid serum reacts positively against Gärtner's bacillus enteritidis. Durham has confirmed this observation. In his study of an epidemic of meat-poisoning at Oldham he found that the sera of 5 of 29 cases of infection with B. enteritidis gave minimal traces of reaction against the typhoid bacillus at 1 : 100, and in lower dilution some of them gave well-marked clumping with typhoid cultures. Hence, he states that "in the absence of differential tests they might have been returned as having been obtained from typhoid fever patients." In another place he makes an even stronger statement based upon tables he gives, that, for the cases examined, in dilutions "lower than and including 1 : 100 it is imma-

terial whether true typhoid or Gärtner's bacillus is used to obtain the typhoid reaction." He adds that "sera obtained from typhoid fever patients are not potent enough to give absolute indications either for diagnosis of bacilli or the nature of serum."

In our case the serum reacted with the typhoid bacillus at 1 : 20, though only partially and imperfectly at the end of an hour, and failed entirely at 1 : 40 and 1 : 80 with another typhoid culture. In Gwyn's case his paracolon was agglutinated by typhoid sera of high potency

FIG. 1.

Gas formation in 2 per cent. glucose broth.



Coli communis. Case 7. Typhoid.

(1 : 300 to 1 : 1100) in dilutions up to 1 : 5. One typhoid serum (potency 1 : 900) gave an incomplete reaction at 1 : 30.

Moreover, Gilbert and Fournier and Achard and Bensaude have shown that B. psittacosis is agglutinated by typhoid sera at 1 : 10, but not at 1 : 40 to 60.

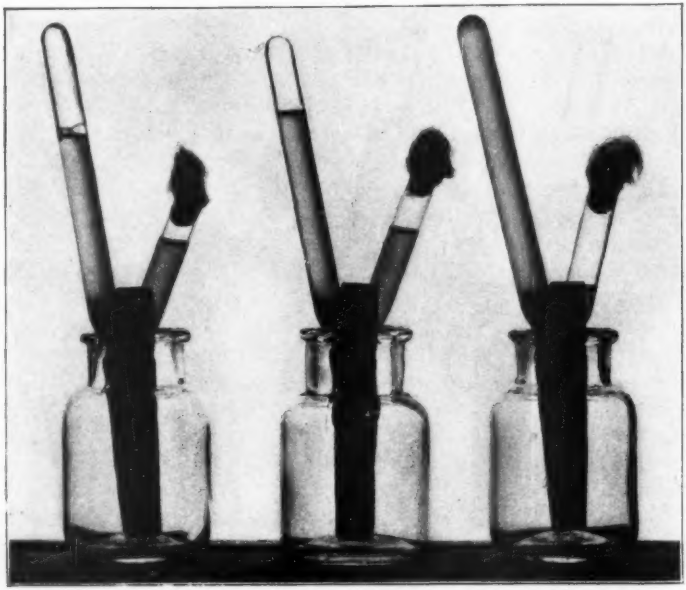
Hence, it cannot be too strongly insisted upon that the ordinary routine test for the Widal reaction give place to more reliable and scientific methods. Dilutions of sera should be high, rarely or never less than 1 : 50, and in the absence of a positive reaction the serum

should be tested against several of the intermediates. Not until this is done will the data of the serum reaction in typhoid fever possess scientific value.

Bacteriological Report. Although the bacteriological work on the bacillus in question, here called Case 7, has not been completed, enough has been done to show that it unquestionably belongs to the group intermediate between coli communis and typhoid, and that among the intermediates themselves it resembles Cushing's bacillus O

Fig. 2.

Gas formation in 2 per cent. maltose broth.



Coli communis. Case 7. Typhoid.

and Gwyn's (paracolon) bacillus—Durham's group C—more nearly than the B. enteritidis of Gärtner, hog cholera and others—Durham's group D.

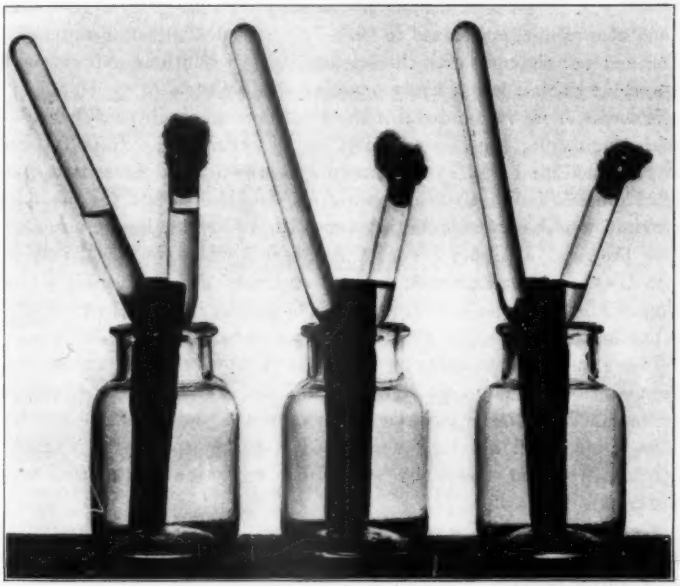
Of the 10 c.c. of blood drawn from the median basilic vein, 4 c.c. was distributed into four Erlenmeyer flasks, each containing 50 c.c. of broth; the remaining 6 c.c. being dropped into six tubes, each one containing 6 c.c. of broth. The flasks and tubes were incubated, and the following day two of the flasks appeared turbid. On the third day the other two flasks and one of the tubes were cloudy, but the remaining

tubes showed no growth either then or later. This experiment and many other similar ones undertaken by us have shown the necessity for considerable dilution of the blood if positive results are to be looked for. Cole has discussed this point very fully.

The turbidity of the four flasks and one tube was found to be due in each instance to a pure culture of the same bacillus, which at first was taken to be typhoid in spite of the fact that the patient's blood gave no Widal reaction with typhoid cultures, even in low dilutions. This

FIG. 3.

Gas formation in 2 per cent. lactose broth.



Coli communis. Case 7. Typhoid.

absence of reaction at that time was ascribed to the early stage of the disease, fifth or sixth day, in which the blood was taken. On testing the bacillus, however, in glucose gelatin it was found to produce gas, and this led to further investigations.

In ordinary media, agar, gelatin, and broth, the growth is indistinguishable from typhoid, nor do stained preparations, ordinary or by Gram's method, show any differences.

Hanging Drop. The bacillus is very motile, even more so than typhoid usually is, and in this resembles the bacilli isolated by Schott-

mueller, Kurth, and others. Kurth remarks that his bacilli possess flagella which are larger than those of typhoid and do not show the same peritrichal arrangement. In our bacillus, however, the flagella appear to be precisely similar to those of typhoid.

Serum Reaction. The bacillus was hardly affected by serum of the patient in the early (fifth, or sixth day) stage of the fever, but serum taken on the twenty-seventh day, at which time cultures from the blood were negative, agglutinated the bacillus in high dilutions, reacting toward typhoid cultures only in low, one to twenty dilutions, and even then, slowly and more or less imperfectly.

Later on the dried blood of the patient agglutinated cultures of Cushing's O and Gwyn's paracolon, but in somewhat lower dilutions. The blood of a rabbit immunized to Case 7 by repeated subcutaneous injections reacted strongly with the bacillus in high dilutions, and also with O and Gwyn, but was entirely negative with cultures of typhoid.

It seems, however, doubtful if the serum reaction will prove of value in distinguishing the intermediates as an entire group from typhoid on the one hand and coli communis on the other. It is true that Schottmueller found that his bacilli (six) would interact for the most part and that Kurth reports the same with his two cultures, but Durham prepared a highly potent Gwyn serum which reacted 1 : 20,000 with Gwyn, but had no effect upon O in 1 : 100 dilutions, and Cushing himself observed that the serum of his O patient reacting 1 : 8000 with O bacillus had but slight effect upon Gwyn's bacillus at 1 : 10.

These observations so far as O and Gwyn are concerned are at variance with our own, but we find with Durham that interactions between the members of the enteritidis group cannot be depended upon: Cultures which could not be distinguished either morphologically or biographically when tested by serum for agglutination showed very marked differences.

Gas Formation. The photographs show, better than a description could do, the gas formation in glucose and maltose and the absence of it in lactose broth.

In this respect Case 7 is typical of the intermediates, all observers agreeing that they do not form gas in lactose or saccharose media. So far as saccharose goes the gas test is of no value, since many true colon bacilli are also unable to ferment it. Durham, indeed, divides the colon bacilli into two groups, coli communis verus, which does not, and coli communis communior, which does ferment saccharose. The photographs show less gas formation on the part of Case 7 than of coli communis. This difference, however, is not constant, and the same may be said of the other intermediates so far tested.

Milk is not coagulated. Schottmueller lays great stress on the fact that among the intermediates there is initial acidity in the milk, fol-

lowed by alkalinity, which in two or three weeks may reach such a point that the casein is dissolved and the milk becomes opalescent. Cushing observed the same thing. This partial clearing was found to occur with B. enteritidis and O, but not with Gwyn or Case 7.

Potato. The growth is slight and there is no discoloration, so on this medium the bacillus resembles typhoid.

Litmus whey is a medium on which Durham places great reliance, but experiments with Case 7 have led to no particular results. It clouds the whey slightly and turns it acid, while typhoid leaves it clear and forms comparatively little acid, but trials so far have not shown that the intermediates form alkali later on, as claimed by Durham, and by itself it does not seem as if litmus whey would be of much value for differentiation.

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AN ANALYSIS OF SEVENTY-ONE CASES OF TYPHOID FEVER TREATED IN THE CHILDREN'S HOSPITAL OF PHILADELPHIA DURING 1901.[1]

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AND
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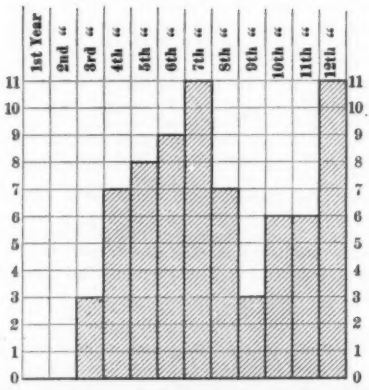
FORMERLY RESIDENT PHYSICIAN.

THE summer of 1901 was marked in Philadelphia by an epidemic of typhoid fever affecting children especially. The number of cases of this disease admitted to the Children's Hospital rose correspondingly, the increase being at a time when the medical wards were under our care, one of us substituting for Dr. Alfred Stengel, to whom, with the other members of the medical staff, Dr. J. P. Crozer Griffith and Dr.

FIG. 1.



Frederick A. Packard, we are indebted for the privilege of analyzing all the cases of typhoid fever that were treated in the hospital during the year. The number analyzed, 71, falls short by 2 of those in the annual report, one of the omitted cases being a convalescent remaining in the wards from the preceding year; the other was a patient admitted with a positive Widal reaction, the temperature, 100° F., falling to normal the next day, and scarlet fever developing two days later, for which she was removed from the hospital.

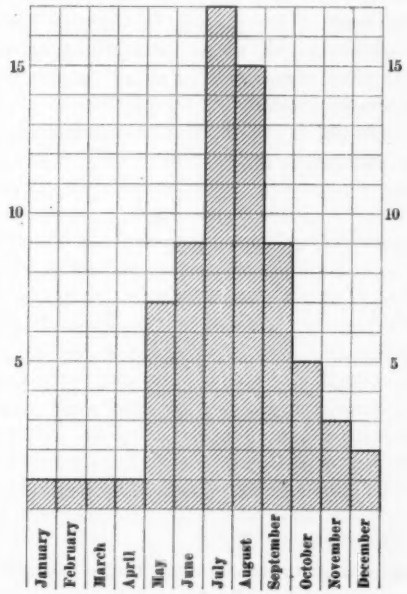
The monthly incidence of the cases is shown by the accompanying chart (Fig. 1).

The sexes showed about the same proportion as in adults, 42, or 59.1 per cent., being boys, and 29, or 40.9 per cent., girls.

[1] Read before the Medical Society of Germantown, January 27, 1902.

Figure 2 shows some interesting features with regard to the ages of the patients. In spite of the fact that the baby ward, with a capacity of twelve beds, was constantly filled all the summer, there was no case under two years of age which aroused even the suspicion of typhoid fever, although careful watch was kept for such a case. The cases showed a decided increase after the age of two years, the maximum being reached between six and seven years of age; in seeking for an explanation of this and of the drop between eight and nine years of age, it seems reasonable, although the number of cases is not very great, to attribute the increase to the digestive disturbances which are of so

FIG. 2.



frequent occurrence between the shedding of the milk teeth and the eruption of the permanent teeth. When these digestive disturbances have subsided there seems to be a period of relative insusceptibility for a year or two, but the age limit (twelve years) for admission to the hospital makes it impossible to say whether or not the second increase continues through later childhood and puberty to the highly susceptible period of early adult life.

Sixty-five of the children (91.55 per cent.) were white, the remaining six being colored. The figures are too small to form the basis of any inference as to comparative racial susceptibilities, but it is interesting

to note that the proportion of colored children (8.45 per cent.) is curiously almost exactly that present in the total number of admissions for all causes (8.49 per cent.).

A study of the city wards from which the patients came showed nothing unusual in the distribution. Dividing the part of the city between the Delaware and Schuylkill Rivers into quarters, using Broad Street as the north and south line, and Market Street as the east and west, nine patients came from the northeastern, three from the northwestern, twenty from the southwestern, and twenty-nine from the southeastern, with ten from West Philadelphia, which figures correspond closely to the general proportions in which the hospital draws its cases from these sections. The series serves, at least, to illustrate the widespread prevalence of the disease in the city and the practical impossibility of attributing the source to anything else than the water-supply. It is therefore earnestly to be hoped that the filter plants now building will be speedily completed.

With reference to the day of the disease on admission—

1	was admitted on the	1st day.
2	were " "	2d "
2	" " "	3d "
6	" " "	4th "
4	" " "	5th "
8	" " "	6th "
19	" " "	7th "
5	" " "	8th "
2	" " "	9th "
2	" " "	10th "
2	" " "	11th "
1	was " "	12th "
2	were " "	13th "
8	" " "	14th "
3	" " "	15th "
1	on each of the (inclusive)	16th to 19th "

The prodromal symptoms as obtained by the resident physicians at the time of admission were, in the order of frequency, as follows:

Fever in	71	=	100 per cent.
Headache in	50	=	70 "
Diarrhœa in	36	=	50 "
Abdominal pain in	23	=	32 "
Constipation in	21	=	30 "
Vomiting in	19	=	26 "
Nose-bleed in	13	=	18 "
Delirium in	5	=	7 "
Chill at onset in	2	=	2.8 "
Convulsions in	1	=	1.4 "
Diarrhœa with blood in	1	=	1.4 "

The highest temperature observed in the hospital was 106.6° F.									
In	6	cases	the	temperature	was	over	.	.	. 106
In	16	"	"	maximum	was	between	.	105°	and 106
In	25	"	"	"	"	"	.	104	" 105
In	11	"	"	"	"	"	.	103	" 104
In	6	"	"	"	"	"	.	102	" 103

While in one case, admitted on the fifteenth day, with enlargement of the spleen and a positive Widal reaction, the temperature was 100° F. on admission, and fell to normal in two days.

The shortest course which the fever ran was nine days in one case, while the longest was forty-four days. The temperature reached normal on an average after twenty-four and one-third days. Of the cases going on to recovery the shortest stay in the hospital was eleven days, the longest was eighty-two days, with an average stay of thirty-six days.

After admission to the hospital the patients presented the ordinary symptoms of typhoid fever in the following frequency :

1. *Widal Reaction.* This was positive in fifty-six out of sixty-four cases, no test being recorded in seven. The percentage of the cases giving the reaction was 87.5 per cent., and this would probably have been much greater if more frequent tests had been made in the negative cases. Thus in but one case were three tests made, each with a negative result, the days not being recorded. In one other case negative results were obtained on the fifteenth and seventeenth days. In the other cases but one test was made, with a negative return, on the sixth, ninth, tenth, twelfth, and seventeenth days, respectively. The reaction is thus, in our experience, the most frequent positive symptom of typhoid fever, but we hasten to add that when it is negative it is not of great value in excluding typhoid fever, provided that other symptoms point to the existence of the disease. Thus two of our patients were sisters, both looking on admission like typhoid fever ; the younger one's attack ran a mild course, without spots or enlargement of the spleen, and with the Widal reaction negative until after defervescence, when it was instantly positive on the twenty-seventh day ; the older sister had a severe attack, with high fever (maximum 106° F.), enlarged spleen and spots, the Widal reaction being negative repeatedly during the first attack, the first positive result being obtained on the twenty-seventh day, or the tenth day of the relapse. A similar case was that of a colored girl, aged seven years, admitted on the sixth day, having had fever, epistaxis, diarrhœa, abdominal pain, and headache ; the symptoms in the hospital were high, continued fever, bronchitis, rigidity of the neck, exaggerated knee-jerks, ankle clonus, Kernig's sign negative, splenic dulness increased, but spleen not palpable, constipation, coated tongue, moderate leucocytosis, 12,600, the

Widal tests being negative on the seventh, tenth, twelfth, and sixteenth days; after a few days of apyrexia a relapse started, and the Widal reaction was found to be positive on the twenty-fifth and forty-second days from the start of the first attack.

2. *Enlargement of the Spleen.* This was present in fifty-nine, or 83 per cent. of the cases, and was usually easily recognizable, the nose of the organ being felt either just under or, more frequently, below the costal border; the largest downward projection observed was 4 cm. from the edge of the ribs. In some of the cases diagnosis of the enlargement rested on increase in the area of splenic dulness, while in a few it was necessary to rely on tenderness. Enlargement of the spleen is, however, so easily detected in children that we accept unhesitatingly the statement in the notes of twelve cases, "spleen not enlarged."

3. *Spots.* Of the sixty-five white children fifty-two, or 80 per cent., showed typical spots, the eruptions not being profuse in the cases under our care. In one case the eruption was confluent, the case being of average severity, judging from the notes and the length of the febrile course.

4. *Constipation* was present in thirty, or 42 per cent., of the cases, a slightly greater number than those with *diarrhœa*—twenty-seven, or 38 per cent.

5. *Coating of the tongue* is mentioned in but twenty-three, or 32 per cent.; the unimportance of this symptom is probably one reason for its passing unnoted, but it is not infrequent to see a child's tongue remain clean throughout the course of the disease; on the other hand, we have seen in children tongues as dry, brown, and fissured as in adults.

6. *Delirium* was sufficiently marked in eleven cases to be worthy of note, the male sex showing a preponderance more marked in the violence than in the number, seven of the patients being boys, or 16.9 per cent. of the males, the remaining four girls being 13.7 per cent. of the female cases.

7. *Intestinal hemorrhage* occurred in four cases, the amount of blood in the stools of three being very slight and scarcely enough to be called a complication; in one case there were three passages, each containing considerable blood, but without any shock or interruption to the favorable course of the case.

8. *Nose-bleed* was noted in three cases.

9. *The diazo-reaction* was tried in seventeen of our own cases, and was negative in but one, this case also failing to give a positive result in three Widal tests, but presenting a remittent fever-curve, spots, and an enlarged spleen. As an illustration of the value of the test in one case admitted as pneumonia, with consolidation of the right apex and pneumococci in the sputum, a positive reaction on the eighth day was the first indication of a typhoid infection which ran a typical course.

Thirteen, or 18 per cent., of the cases had complications. In half of these otitis media occurred, being associated in one case with pneumonia, in one case with alveolar abscess and caries of the jawbone, and in one case with a perirectal abscess. The other complications were cervical adenitis, without suppuration, in one case, and with it in another; jaundice in one case; pustules twice; furuncles in one case; abscess, vaginitis, and nephritis in one case; noma in one case, ending fatally; diphtheria in one case, which was removed to the Municipal Hospital, where it died; a prolonged cystitis existed in one case during convalescence, and the urine, collected as aseptically as possible, contained many bacteria; a culture on agar gave a growth of a bacillus which was actively motile; in a hanging-drop agglutination and cessation of motion were observed on the addition of a blood-serum known to give the specific typhoid reaction.

Relapses were seen in six patients, or 8.5 per cent., starting on the seventeenth, twenty-second, twenty-ninth, thirty-fourth, and forty-first days, respectively. In these cases the primary attack was severe in one, moderate in one, and mild in all the others.

The deaths numbered three, a mortality of 4.2 per cent. One case died of noma, one of diphtheria, and one of toxæmia, the mortality, therefore, of uncomplicated typhoid fever in this series being less than 1 per cent.

The routine elements of treatment in the cases under our care consisted of rest in bed and a liquid diet. Not knowing of any specific for the disease, the treatment was to a certain extent symptomatic. Using the temperature as an indication of the degree of toxæmia, an endeavor was made to combat the effects of the poison and to secure its elimination by hydrotherapy. This was started in the majority of cases as a tub bath, the temperature of the water being 85° F. A cloth wrung out of ice water was put on the child's head and the body immersed in the bath, the duration of which was from five to ten minutes, the influence on the temperature and on the pulse being the guide; while in the water the surface of the body was gently rubbed by the hands of the nurses. In a few cases, especially among the younger children, the tub baths were not well borne, and sponging with water of the same or higher temperature was substituted. Sponge baths were adopted at the start in some cases, but they often failed to influence the temperature sufficiently, the tub baths being used later with good effect.

As an added means of elimination we used in about twenty-five of the cases drachm doses of the solution of the citrate of potash well diluted with water, with the hope also that it would protect the kidneys from the poison as it passed out; we cannot, of course, assert that the medicine was of any more value than the water, but no deleterious effect was seen.

In those cases with loose movements an attempt was made to lessen the enteritis by giving bismuth salicylate, in doses of three grains, every three hours, sometimes combined with the subnitrate; in this we seemed successful. The salicylate was chosen first with the hope that its antiseptic properties might in some degree lessen the activity of the specific germs in the intestinal canal, but from the course of the cases we cannot see that our hopes were fulfilled.

Whiskey was given in almost every case. Without entering into a discussion as to the food value of alcohol or how it acts in fever, we feel sure that many of the cases were visibly benefited by it. The doses ranged from thirty drops for the younger children to one, or, in a few cases, two drachms for the older children every three hours. This was usually given at the same time with the milk, but sometimes the dose was divided, half being given before and half after the bath. In no case was it pushed until the odor could be detected on the breath.

Strychnine was occasionally used as a heart tonic, and one or two cases with heavily coated tongues received turpentine in five-drop doses. Children entering before the eighth day of the disease were given divided doses of calomel until a grain had been taken; after this constipation was overcome with the use of enemas.

Liquid diet was continued for ten days after defervescence was completed, the first addition to the diet being usually milk toast. Convalescence was aided by strychnine and Basham's mixture; if the tongue remained coated it was made to clear by No. 12 of the hospital pharmacopœia, a mixture of bicarbonate of soda and compound infusion of gentian. As soon as each patient was able to sit up he was sent to the country branch of the hospital, where the life out-of-doors in fresh air accomplished complete restoration to health.

In conclusion, our impression is that while typhoid fever may sometimes run a very mild or even abortive form in children, yet its clinical picture does not differ from that in adults in any essential feature save in the somewhat lower mortality.

THE FREQUENCY OF HEREDITY IN GASTRO-ENTERIC DISTURBANCES.

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Great stress is laid upon the heredity of tuberculosis, syphilis, or leprosy, but many questions are yet unanswered concerning the heredity of cancer and other diseases. Gout, diabetes mellitus, and obesity are considered a trio which can be followed through generations. The pedi-

gree of bleeders can often be traced to remote ancestry; and nervous disposition as well as mental diseases of ancestors are for many the cause of a gloomy view into the future. The pathological substrata of these hereditary troubles are yet unknown, and even the question whether the bacillus tuberculosis can be transmitted from parent to offspring has not yet been fully solved.

In order to avoid any difficulty or misunderstanding in dealing with these questions, science has introduced the expression "hereditary predisposition." Thus some people have a tendency to catarrh of the nose and throat; the same sensitiveness to "colds" was observed in their sires.

The scientific value of the expression "catching cold" was for a long time denied, until Birch-Hirschfeld, in his *General Pathology*, adduced sufficient proof of its substantial anatomico-pathological foundation.

If disturbances of circulation in the mucous membrane or anomalies of development are really traced in father and son, the same weakness of cells in one or several tissues will be common to both.

If in most nervous diseases the anatomico-pathological changes in the nerve cells have not yet been demonstrated it is to be believed that the deviation from the normal is an hereditary tendency. As a German proverb says, "The apple does not drop far from the tree;" certain laws must obtain in these cases, and no investigator dares to call it chance. Because science to-day is not advanced enough to prove this it does not follow that no light will ever be thrown upon this subject.

The expression "the power of resistance" of the organism has a complicated meaning. In the sense of Darwin's teaching this resistance is the principal factor in the survival of the fittest. At the same time another equally important factor is the "capacity for adaptation," which also is an expression for an aggregate of single facts. The study of the cell inheritance is left to the future.

Even the Roman fable teaches us that the health of the stomach was considered a factor of the first order and a principal condition of the general health. The organism, as a result of modified digestion, must needs show changes which are not visible to the naked eye. The fact that man can live a certain length of time without a stomach changes nothing. The man deprived of his stomach must succumb in the struggle for existence.

The comparative analysis of healthy stomachs, according to Boas' test meal, have shown a total acidity of 50 and 30 free HCl, together with a certain motile power and a capacity for absorption; yet a large number of people with strong deviation from this normal line do not at all consider themselves as stomach patients. They never think of consulting a specialist in order to obtain an analysis of the gastric juice. If they are ill they are treated on general principles, without special consideration of the peculiarities of their stomach, which they may have inherited from their ancestors.

The fact that I have often found in blood relations the same dyspeptic conditions induced me to study the question more closely in order to determine whether or not a direct inheritance not only of pronounced digestive troubles, but also of slight deviation from the normal, could be traced.

We speak of "predisposition," and are apt to forget that in such instances substantial pathological changes are inherited, which result in an organism with a much diminished power of resistance. If a so-called healthy stomach shows 35 total acidity only this deficiency must of necessity find expression somewhere in the system.

In order to change into useful values such terms as "disposition," "anomalies of constitution," etc., their single factors should be tested numerically. This opens a wide field to science in the future.

Unfortunately, the physician finds it difficult to persuade these so-called healthy people with an occasional disturbance of health to be thoroughly examined. Given the physiological limit of 20 to 40 free HCl, a person who is always in the vicinity of 20 cannot help being influenced by it. This is clear from a mathematical point of view. People with constantly low figures will suffer more easily from disturbances than those with an average of 30 free HCl.

On the other hand, people with 40 HCl, given the same conditions, will more readily develop superacidity.

The fact that these disturbances do not occur upon slight provocation is accounted for by the power of compensation. The personal description of the symptoms of a patient suffers usually from an involuntary want of precision.

In no histology do we see mention of a special nervous sensory apparatus of the stomach. The taste bulbs do not extend beyond the pharynx. A sweet, bitter, sour, or salty taste cannot be experienced by the stomach. Then there remain only painful sensation and tactile impressions which convey perception of temperature and pressure sensation.

Landois says, "It is highly probable that the sensory and tactile nerves possess different nerve endings."

The sensation of temperature, according to Landois, ceases in the œsophagus. Quincke states that even great variations of temperature are hardly perceived in the stomach. Pain, however, can occur wherever there are sensory nerves.

If, then, we have neither taste nor finer appreciation of temperature in the stomach, it follows that we can only perceive sensations of pain and pressure. This explains why patients cannot correctly describe sensations experienced in their stomachs.

If a strongly acid gastric juice gets into the œsophagus or reaches the tongue the patient can experience it. Further, if the pain is of a

pronounced character there is no mistake in the statement. A superacidity without eructation can only be described by the patient as a painful sensation, perhaps with the words "burning in the stomach." The other sensation is pressure, which can be caused by irritation of sensory nerves, with normal contents of the stomach, or by abnormal contents with normal nerves. A moderate degree of pain and sensation of pressure can so intimately pass into each other that they cannot be described accurately.

Einhorn has recently published six cases of achylia gastrica which presented all the symptoms of superacidity, with burning. Not only have I had similar cases under observation, but have heard patients describe a nervous subacidity and atony, with subacidity as superacidity.

In order to study the question of gastric analysis in blood relations, I have looked over the material at my disposal during the years 1898, 1899, and 1900. Analysis of test-meals showed the following:

Gastritis acuta		1	
Gastritis chronica		53	
Achylia gastrica		18	
Ulcus ventriculi		5	
Carcinoma ventriculi		10	
Enteroptosis (male)	*a.* anacida	0	5 cases.
	b. subacida	2	
	c. normalis	1	
	d. superacida	2	
Enteroptosis (female)	*a.* anacida	1	99 cases.
	b. subacida	33	
	c. normalis	40	
	d. superacida	25	
Gastroptosis (male)	*a.* anacida	1	12 cases.
	b. subacida	4	
	c. normalis	0	
	d. superacida	7	
Gastroptosis (female)	*a.* anacida	1	45 cases.
	b. subacida	14	
	c. normalis	9	
	d. superacida	21	
Gastrosuccorrhœa hyperacida contin.		9	11 cases.
" " periodica		2	
Atonia ventriculi	*a.* subacida	24	64 cases.
	b. normalis	23	
	c. superacida	17	
Ectasia		8	
Superaciditas nervosa		83	
Gastralgo-kenosis		7	
Gastralgia		1	
Regurgitatio nervosa		2	
Dyspepsia nervosa		8	
Neurasthenia *a.* anacid		1	42 cases.
b. subacid		24	
c. normal		17	
Enteritis acuta		2	
" chronic		4	
		480	

Brought forward	480	
Gastro-enteritis acuta	1	
" " chronica	8	
Diarrhœa nervosa	2	
Colitis membranacea hyperac.	1	4 cases.
" "	3	
Dysenterica tropica	1	
Atonia intestin.	3	
Constipatio chronica	13	
Ulcera recti	1	
Colitis	3	
Carcinoma recti	1	
Cirrhosis hepatis	2	
Carcinoma hepatis	1	
Cholelithiasis	7	
Perihepatitis	1	
Stenocardia	4	
Vitium cordis	14	
Adipositas cordis	1	
Arterio-sclerosis	1	
Nephritis chronica	3	
" hemorrhagica	1	
Cystitis	1	
Anæmia	8	
" with hyperchlorhydria	2	
Chlorosis	4	
Hysteria	6	
Epilepsia with atonia and subacid.	2	
" " superacid.	1	
Dementia paralytica	1	
Obesitas	1	
Rheumatismus	1	
Arthritis urica	4	
" deformans	1	
Urticaria	1	
Acne	1	
Malaria	2	
" perniciosa	1	
Diverticul. œsophagi	2	
Sarcoma sterni	1	
Phthisis pulmon.	6	
" intestin.	1	
Typhus abdom.	3	
Lues	1	
Total number of cases	603	

In the order of frequency, the following table was arranged:

Enteroptosis in women	99
Superaciditas nervosa	83
Atonia, both sexes	64
Gastritis chronica	53
Gastroptosis (female)	45
Neurasthenia with variable analyses	42
Achylia gastrica	18
Vitium cordis	14
Constipatio chronica	13
Gastroptosis (male)	12
Gastrosuccorrhœa	11
Carcinoma ventriculi	10
Ectasia	8
Dyspepsia nervosa	8
Anæmia	8

These statistics show 166, or about one-third of all cases, to be hyperchlorhydria. This percentage is somewhat smaller than Einhorn's statistics for New York, or Hemmeter's for Baltimore. Kövesi, of Budapest, found the same. This author, in an article in vol. v., *Arch. für Verdaungskr.*, mentions 98 as the highest figure of total acidity, and thinks the figures of other authors—100 to 150—excessively high. My average figures are 80 to 110. One case came under my observation with the incredible figure 237, but this occurred only once.

Gastroptosis and enteroptosis occurred in 144 females and 17 males, or in 24 and 3 per cent., respectively, of all my cases. Boas has recently stated that atony, scientifically proved (Mathieu's method), is not nearly as frequent as is usually supposed. For the purpose of comparison I made the following observations: In Berlin I saw, within two weeks, 2 cases of atony among 70 cases at Boas' Poliklinik—about 3 per cent. In Washington I examined, in five weeks, 30 cases, according to Mathieu, and found 7 cases, with food remnants of over 200 c.c., making a percentage of 23.4.

During more extended observations these numbers will vary; so, for instance, for Washington it would be reduced to 10.7 per cent.

Having given a general outline of my material, I will now endeavor to give a short sketch of all those cases where I had the opportunity of examining blood relations.

The total acidity was determined by the usual method. The figures of free HCl have not been calculated into percentage, but are expressed in centimetres of $\frac{1}{10}$ NaOH as found in titration, and with dimethylamidoazobenzol as an indicator. The cases have been divided into two groups—

1. Those without similarity of analysis or disease.
2. Those with pronounced similarity of analysis, of disease, or of both.

Class I. *No Similarity.*

Family 1. (*a*) Father, aged sixty years, mitral insufficiency; has died since. Total acidity, 40; free HCl, 10; subacidity. (*b*) Daughter, chronic constipation and enteroptosis; total acidity, 44; free HCl, 24. (*c*) Son, aged about twenty-two years, complains of superacidity, mild constipation; total acidity, 80; free HCl, 45.

Family 2. (*a*) Mrs. C., woman in middle life; pronounced catarrh of nose and throat. Every morning her pillows are saturated with bloody mucus. The lower border of her stomach is five fingers below the umbilicus. Total acidity, 40; free HCl, 6; alizarin test, 30; enteroptosis, subacidity. (*b*) Daughter, nervous superacidity. Total acidity, 82; free HCl, 42.

Family 3. (*a*) Miss M., tuberculosis pulmonum; has died since. Total acidity, 40; free HCl, 16. (*b*) Brother, no tuberculosis; melancholia. Total acidity, 96; free HCl, 64; superacidity.

Family 4. (*a*) Mr. H., old gentleman, with asthmatic thorax. Total

acidity, 38; free HCl, 5; catarrhus ventr. chronicus. (*b*) Son, nervous dyspepsia. Has been cured of nervousness by hydrotherapeutics by Professor Winternitz. Total acidity, 63; free HCl, 30.

Family 5. (*a*) Mrs. C., medium-sized, under-nourished. Lower border of stomach three fingers below umbilicus. Right kidney palpable by one-half. Examination by diaphany. Total acidity, 80; free HCl, 48; enteroptosis, superacidity. (*b*) Sister of Mrs. C., subject to nervous superacidity. Total acidity, 50; free HCl, 15.

Family 6. (*a*) Mr. L., aged forty years. His brother, a physician, took him to Garfield Hospital, where he died of carcinoma of the lesser curvature. Tumor was palpable. No free HCl; lactic acid; autopsy. (*b*) Miss L., sister of deceased, enteroptosis; also scoliosis. Total acidity, 60; free HCl, 32.

Family 7. (*a*) Mrs. S., aged thirty years, globus hystericus, superacidity complaints, gastroptosis. Total acidity, 73; free HCl, 15. (*b*) Her brother, nervous, suffers from pseudo-angina pectoris. Total acidity, 62; free HCl, 48.

Family 8. (*a*) Mr. T., young man, with slight complaints of superacidity. Total acidity, 66; free HCl, 32. (*b*) His father, chorea as a child; even yet convulsive contractions of certain muscles; slight disturbances of articulation. Total acidity, 10; free HCl, 0; no ferments; achylia gastrica.

Family 9. (*a*) Miss B., severe enteroptosis, with acute exacerbations. Total acidity, 45; free HCl, 15; subacidity. (*b*) Father of Miss B., neurasthenia. Total acidity, 38; free HCl, 12; subacidity.

Family 10. (*a*) Miss G., suffers from constipation. Examination by diaphany, gastroptosis. Had typhoid fever in the course of the year. Total acidity, 54; free HCl, 30. (*b*) Miss G.'s brother, pronounced superacidity. Total acidity, 108; free HCl, 58.

Family 11. (*a*) Mrs. D. F. Total acidity, 3; achylia gastrica. (*b*) Daughter, enteroptosis with superacidity. Total acidity, 78; free HCl, 42.

Family 12. (*a*) Miss G., beginning enteroptosis. Total acidity, 60; free HCl, 30. (*b*) Brother suffers from malaria and dyspepsia. Total acidity, 53; free HCl, 26.

Family 13. (*a*) Mrs. S., of French descent; highly nervous. Total acidity, 30; free HCl, 0; subacidity nervosa. (*b*) Son, very nervous; suffers from superacidity. Total acidity, 90; free HCl, 40. (*c*) Miss S., floating right kidney, fourth degree; severe enteroptosis; emaciated person; no analysis.

Family 14. (*a*) Miss S., anæmia. Total acidity, 64; free HCl, 34. (*b*) Her brother, with nervous dyspepsia, complains of superacidity. Total acidity, 60; free HCl, 32. This family might be included in the next class, which deals with cases of blood relations *with similarity*.

Class II. *Similarity.*

Family 1. (*a*) Mr. D., supposed to have a sound stomach. Analysis showed total acidity, 16; no ferments; achylia gastrica. (*c*) Miss D., sister, has had stomach trouble for years; never yet found permanent relief. Total acidity, 10; no ferments; achylia gastrica.

Family 2. (*a*) Mr. M., artist by profession; subject to petit mal. Total acidity, 72; free HCl, 52; superacidity. (*c*) Mrs. M., mother

of artist, aged about seventy years; nervous; has suffered from digestive disturbances over a decade. Soup and starvation diet were tried in vain. Total acidity, 96; free HCl, 56; superacidity.

Family 3. (*a*) Mrs. W., woman in middle years, of slight frame, very thin, lower border of stomach two fingers below umbilicus. Right kidney movable; very thin abdominal walls; mother of seven children. Various rest and fat cures have been resorted to without avail, since patient seems unable to retain permanently the flesh gained during treatment. Backache and pain in right side; dyspeptic. Report from gynecologist: prolapsus uteri et ovarii dextri. Analysis, total acidity, 20; free HCl, 0; enteroptosis, subacidity. (*b*) Miss W., oldest daughter; medium-sized, quiet temperament, slight backache, first degree of enteroptosis. Total acidity, 38; free HCl, 16; subacidity. (*c*) Miss I. W., second daughter; same type as mother; nervous temperament, seems unable to gain in weight. Right kidney distinctly palpable. After violent exercise on horseback, kidney comes down much lower. Splashing stomach, lower border one finger below umbilicus. Chronic constipation. Total acidity, 48; free HCl, 17; subacidity, enteroptosis. (*d*) Mrs. E., sister of Mrs. W. Quite contrary to her sister, very stout, colitis chronica, gastroptosis; stomach two fingers below umbilicus. Test-meal food remnants, 220 c.cm. Total acidity, 90; free HCl, 25; gastroptosis, atony, colitis, superacidity. (*e*) Miss E., daughter of Mrs. E.; type of her cousin, not her mother; slender, less than medium height, nervous, anæmic. Total acidity, 50; free HCl, 14; alizarin value, 40; subacidity. (*f*) Miss E., niece; brother's child; chronic severe anæmia, palpitation, dyspepsia. Total acidity, 52; free HCl, 18; alizarin, 40; subacidity.

Family 4. (*a*) Miss F. For six years continual loss of weight. Headache, with nausea, severe constipation, amenorrhœa. Examination by gastrodiaphany shows stomach three fingers below umbilicus; right kidney palpable. Total acidity, 88; free HCl, 43; enteroptosis, superacidity. (*b*) Miss F. II., younger sister; colitis membranacea, erosiones ani. (*c*) Miss F. III., enteritis chronica.

Family 5. (*a*) Mr. W., nervous young man; complains of burning in stomach, weakness, anxiety; afraid of appendicitis. Total acidity, 90; free HCl, 36; superacidity. (*b*) Mrs. W., mother of young man; chronic headache since childhood; has sudden sensations of hunger, vomiting of bile; fears to have inflammation in region of stomach; right kidney movable; lower border of stomach three fingers below umbilicus. Total acidity, 82; free HCl, 36; enteroptosis, superacidity.

Family 6. (*a*) Mr. S., man in middle life; has suffered for ten years from gastrosuccorrhœa, superacidity periodica; 300 c.cm. of clear gastric juice often present. Total acidity, 100; free HCl, 72; superacidity, gastroptosis. (*b*) Mrs. M., his sister; lower border of stomach five fingers below umbilicus. Total acidity, 32; free HCl, 16; gastroptosis, subacidity.

Family 7. (*a*) Miss R.; lower border of stomach almost at symphysis. Total acidity, 63; free HCl, 22; enteroptosis. (*b*) Miss J. R.; lower border of stomach two fingers below umbilicus. Total acidity, 70; free HCl, 36; kidney not movable; gastroptosis.

Family 8. (*a*) Colonel H., a neurasthenic old gentleman; has been repeatedly in the hands of nerve specialists in Europe; insomnia. Total acidity, 38; free HCl, 7; lower border of stomach two fingers

below umbilicus; gastroptosis, subacidity. (*b*) Miss H., daughter; nervous. Total acidity, 40; free HCl, 10; subacidity.

Family 9. (*a*) Miss A.; anæmic, chronic headache. Total acidity, 30; free HCl, 5; gastroptosis, subacidity. (*b*) Mr. A., brother; pronounced gastroptosis, arrhythmia. Total acidity, 64; free HCl, 33. (*c*) Mrs. A., mother; chronic headache for number of years; marked gastroptosis. Total acidity, 80; free HCl, 64; superacidity.

Family 10. (*a*) Miss M., teacher; enteroptosis; has been treated for years for displacement of uterus and ovaries. Total acidity, 54; free HCl, 27. (*c*) Mrs. M., mother; gastroptosis, fissura ani, gastro-enteritis chronica. Total acidity, 37; free HCl, 2; subacidity.

Family 11. (*a*) Mrs. P.; gastroptosis; examined by diaphany; hemorrhoids. Total acidity, 54; free HCl, 12; subacidity. (*b*) Miss P., daughter; pronounced enteroptosis. Total acidity, 48; free HCl, 24.

Family 12. (*a*) Miss G., examined by diaphany; enteroptosis; superacidity; enteritis chronica. Total acidity, 99; free HCl, 56. (*b*) Miss G., sister. Total acidity, 82; free HCl, 28; slight gastroptosis, superacidity.

Family 13. (*a*) Miss W.; enteroptosis; right kidney movable. Total acidity, 72; free HCl, 41; superacidity. (*b*) Mrs. W.; constipation; hyperchlorhydria. Total acidity, 78; free HCl, 42.

Family 14. (*a*) Miss H. P.; enteroptosis; examination by diaphany. Total acidity, 67; free HCl, 32. (*b*) Miss E. P.; enteroptosis; right kidney freely movable. Total acidity, 40; free HCl, 20.

Family 15. (*a*) Prof. B.; pronounced symptoms of superacidity. Total acidity, 96; free HCl, 60; alizarin value, 86. (*b*) His brother, editor of daily paper. Total acidity, 72; free HCl, 52; alizarin, 46; superacidity. It is an interesting fact that Prof. B.'s wife also suffers from superacidity. Total acidity, 70; free HCl, 36; alizarin, 64.

Family 16. (*a*) Miss N. Total acidity, 50; free HCl, 35; constipation, enteroptosis. (*b*) Miss J. N. Total acidity, 45; free HCl, 20; acne, slight gastroptosis. (*c*) Father; enteritis chronica.

Family 17. (*a*) Mr. P.; chronic constipation. Total acidity, 50; free HCl, 30. (*b*) Miss P.; constipation, slight gastroptosis, superacidity. Total acidity, 72; free HCl, 36. (*c*) Miss P., cousin; severe chronic constipation, superacidity. (*d*) Miss P., sister; enteroptosis of fourth degree.

Family 18. (*a*) Miss McK.; chlorosis, chronic headache. Total acidity, 36; free HCl, 18; alizarin, 10; subacidity. (*b*) Miss McK., sister; anæmia. Total acidity, 64; free HCl, 20. (*c*) Mr. McK., father; repeated attacks of malaria, anæmia; analysis not made.

Family 19. (*a*) Mrs. von D.; catarrhus chronicus. Total acidity, 30; free HCl; alizarin, 19. (*b*) Mrs. F., sister; suffers from enteroptosis. Total acidity, 36; free HCl, 10; subacidity.

Family 20. (*a*) Miss F.; chronic constipation. Total acidity, 45; free HCl, 20. (*b*) Mr. F., brother; chronic constipation for eighteen years. Total acidity, 47; free HCl, 24.

Family 21. (*a*) Mr. E., young man of large frame, wanting in energy. Total acidity, 72; free HCl, 40; superacidity. (*b*) Mrs. E.; acute peristaltic disturbances after excitement. Total acidity, 54; free HCl, 40. (*c*) Mr. E., eldest son; subject to neuralgia, superacidity; leads a gay life as a student. Total acidity, 80; free HCl, 50.

Family 22. (*a*) Mr. M.; suffered for many years from pain in region

of gall-bladder; the latter is very sensitive on pressure; chronic colitis. Patient rarely has severe attacks of pain; smokes and drinks heavily. Total acidity, 72; free HCl, 34; alizarin, 48. Repeated attacks of icterus, superacidity. (*b*) Miss M., daughter; same complaint as father, only pain more frequent in region of gall-bladder. At times acholic stools. Total acidity, 60; free HCl, 30; alizarin, 49; cholelithiasis.

Family 23. (*a*) Mrs. S., widow of a physician; very energetic woman, who inclines to overwork and then becomes nervous; lower border of stomach three fingers below umbilicus. Total acidity, 104; free HCl, 60; gastroptosis, superacidity. (*b*) Mrs. M., younger sister of Mrs. S.; very nervous in her youth; both ovaries, although healthy, were removed; symptoms remained the same. Total acidity, 86; free HCl, 34; enteroptosis, superacidity. (*c*) Miss S., daughter of Mrs. S.; anæmic; bruit de diable; chronic headache; lower border of stomach one finger below umbilicus. Total acidity, 78; free HCl, 26; mild gastroptosis, superacidity.

Family 24. (*a*) Miss B., young lady of strong physique. After violent gymnasium work develops symptoms of enteroptosis; lower border of stomach one and a half hand below umbilicus. Examination with gastrodiaphany shows an almost vertical position of the stomach. Right kidney movable; right ovary displaced downward and highly sensitive. Gynecologist proposed operation, which was refused, and a successful "mast kur" was made instead. Total acidity, 46; free HCl, 23; enteroptosis. (*b*) Sister; dyspeptic complaints after an attack of enteritis. Total acidity, 44; free HCl, 24. (*c*) Second sister; tachycardia; lower border of stomach one finger below umbilicus. Total acidity, 46; free HCl, 14; mild gastroptosis, superacidity.

Family 25. (*a*) Miss H.; severe anæmia; very slender figure; enteroptosis; repeated operation for retrodisplacement of uterus; operation for fixing kidney. Achylia gastrica. Total acidity, 8; no ferments. (*b*) Mrs. H., cousin, fathers were brothers, same habitus; acute enteroptosis after being thrown during a runaway; weight, 90 pounds; has made repeated rest cures. Total acidity, 24; free HCl, 0. Alizarin, 16. Patient improves until total acidity 36, free HCl 16, is reached. Operation for fixing kidney. Prolapsus and enlargement of the uterus; congested ovaries; subacidity. It is interesting to note that cases *c* and *d*, sister and brother of Mrs. H., represent quite another type. Both are large, corpulent, weighing over 170 pounds. (*c*) Mrs. L. Total acidity, 78; free HCl, 46; superacidity. (*d*) Mr. H. Total acidity, 80; free HCl, 36.

Family 26. (*a*) Mr. D., a middle-aged man; chronic constipation; superacidity; attacks of vertigo. Total acidity, 75; free HCl, 50. (*b*) Daughter of Mr. D.; enteroptosis; lower border of stomach four fingers below umbilicus. Right kidney movable. Total acidity, 96; free HCl, 50; sensitive colon; constipation, superacidity.

Thus we have in toto 40 families, representing 597 cases—14 families without similarity (35 per cent.); 26 families with similarity (65 per cent.).

Enteroptosis and Gastroptosis. Gastroptosis, instead of enteroptosis, is differentiated whenever the stomach alone is displaced downward. Among the families *with similarity* there are 6 families with one

case of enteroptosis each, and 2 families with one case of gastroptosis each. Among the families with similarity there are 2 families with enteroptosis in at least two members of each separate family. There are 9 families in which one member has enteroptosis and one has gastroptosis. Two families show gastroptosis in two members. In 5 families enteroptosis is found but once in each. One family has only one member with gastroptosis. If we consider enteroptosis and gastroptosis as the same clinical picture we find it in several members in 13 out of 40 families, which would appear to justify the conclusion that enteroptosis in one-third of the cases is a family peculiarity. Two hypotheses are admissible as an explanation—either enteroptosis and its tendency is inherited, or similar modes of living produce enteroptosis in different members of the same family.

Among 40 families, 27, or 67 per cent., show cases of enteroptosis. Of the 27 families there are 13, or 48 per cent., families with enteroptosis in various members. In 5 families mother and daughters have enteroptosis. In 8 families sisters and cousins have enteroptosis. In 3 instances (families Nos. 6, 23, and 25) the various members live in different towns; also family No. 16 most of the time. Therefore in 3 families the conditions of life differ, and cannot be taken as an etiological factor.

In families Nos. 3, 24, 25, cases of enteroptosis give a history of violent concussion. In the same families, however, are found other cases of enteroptosis without a traumatic history. Cases Nos. 3 and 23 seem to point strongly to the theory of inheritance. In both families enteroptosis is found in two mothers (sisters) and their children, but the conditions of life are entirely different.

HYPERCHLORHYDRIA. Among 14 families without similarities of symptoms there are 10 families with superacidity. The 26 families with similarity as studied above show 10 families with repeated cases of superacidity, 5 families with one case each, and 11 families in which it is not present.

In a total of 40 families we find 25, or 62.5 per cent., with superacidity; of these in 10 families, or 37.5 per cent., several members were afflicted. Of the 25 families with superacidity 40 per cent. had more than one case in the same family. Of the 10 families showing several cases of superacidity in the same family we have 5 where it occurred in parents and children, and in the other five families in sisters, brothers, and cousins.

In 5 of the 25 families the members suffering from superacidity live in different surroundings and circumstances.

SUBACIDITY. Subacidity is found in 8 out of 14 families which showed no similarity of clinical picture. In one instance it is found among several members of the same family, and yet all were suffering

from entirely different diseases. Among the 26 families with similarity subacidity occurs in 10 families—in 3 families repeatedly in different members; in 6 families 1 each; in 1 family with achylia gastrica.

In a total of 40 families we find 19 families with subacidity—47.5 per cent. In 4 families out of the 40 it is found repeatedly in 10 per cent. Out of 19 families with subacidity it is found repeatedly in 4 families—21 per cent.

ACHYLIA GASTRICA. Among the families without similarity we find achylia twice, but no repeated cases in the same family. In families with similarity we find achylia gastrica in 2 families—in 1 family in several members and in another family with subacidity.

NORMAL ANALYSIS. A total acidity of 40 to 65 was considered normal, but the free HCl must be 20 to 40. Fourteen families without similarity show 7 families with normal figures. Among these 7 families occurred two with normal figures in two of its members, yet the symptoms and complaints are absolutely different. In one case (No. 14) showing a normal analysis the complaints are those of superacidity. The 26 families with similarity include 12 families with normal figures. Four of these 12 families have several members with normal analyses; 19 normal figures—47.5 per cent.; 6 families in several members normal analyses—15 per cent.; 6 families out of 19 have repeated cases of normal analyses—31.5 per cent.

We further find in these families repeatedly:

Anæmia in family	No.	3	Two cousins.
"	"	18	Father and daughter.
Constipation	"	17	" " "
"	"	20	Brother and sister.
Cholelithiasis	"	29	Father and daughter.

RÉSUMÉ.

Enteroptosis in families	67.5	per ct.
Superacidity "	62.5	"
Subacidity "	47.5	"
Normal acidity "	47.5	"

Repeated cases in the same family:

Enteroptosis	32.5	per ct.
Superacidity	37.5	"
Subacidity	10.0	"
Normal acidity	15.0	"

In 27 familes of enteroptosis we find repeated cases	48.0	per ct.
" 25 " superacidity " "	40.0	"
" 19 " subacidity " "	21.0	"
" 19 " normal acidity " "	31.5	"

Enteroptosis is most frequent, but superacidity presents the largest number of cases in the same family. *Of 40 families 23 (57.5 per cent.) have several cases in one family of their characteristic analyses. In other*

words, one family out of every two presents more than one case of digestive disturbance of the same nature.

The average frequency of duplicate cases of enteroptosis, superacidity, subacidity, and normal acidity lies between 27 per cent. and 48 per cent., and is consequently 34.5 per cent.

TUBERCULOUS PERICARDITIS:

FOLLOWED BY REMARKS UPON PARACENTESIS AND INCISION.

By Beverley Robinson, M.D.,
of New York.

Two cases of this somewhat rare disease have been under my care within the past eighteen months. In both cases autopsies were obtained —the one complete, the other only embracing the examination of the heart and pericardium. In one of these instances the pericardium was aspirated several times; in the other it was not considered necessary or judicious to operate. The history of my first case was read at a meeting of the Practitioners' Society,[1] October 11, 1901, and the specimen shown. The case was discussed by the members.

During the past eighteen months I have also taken care of two other cases of pericarditis. Of these, one occurred as a complication of Bright's disease; the other apparently of rheumatic origin. I shall refer to these later in my remarks upon paracentesis.

In certain instances of tuberculous pericarditis it has been noted that there was no evidence of tuberculous deposit in the adhesions which were present. In those instances more numerous, where tubercles are discovered in the adhesions, they may appear like grayish areas at the line of union of the parietal with the visceral layer. In 1048 autopsies, Wells[2] found tuberculous pericarditis 10 times, which formed about 8 per cent. of all cases of pericarditis recorded by him. It is not limited to adults, but may occur quite frequently in childhood or infancy. It is more frequent among men than women. Baginsky reports 15 cases in 4500 autopsies, and of these 4 were purulent. In Osler's autopsies, 1000 in all, there were 7 instances of tuberculous pericarditis.[3]

Welch, in his report from Johns Hopkins Hospital, states he has seen 6 cases. Although often spoken of as frequent, it is not shown by references in *Index Catalogue*, *Transactions of the Pathological Society of London*, etc. Up to 1893 Osler had seen only 17 cases, and yet he writes tuberculous pericarditis follows hard upon the rheumatic form.

[1] Medical Record, November 23, 1901, p. 831.
[2] Journal of the American Medical Association, May 25, 1901.
[3] The American Journal of the Medical Sciences, 1893, p. 20.

In Wells' cases, where the condition was miliary and chronic, there were adhesions and no fluid. In acute miliary eruption, and in those where there was caseous deposit,[1] there was also more or less effusion in the pericardial sac.

In one instance, where no tubercles were shown in a case of acute pericarditis, the inflammation was apparently due to toxins of tubercular origin. This opinion was supported by the fact that tubercles were found extensively in other viscera. The tuberculous cases, especially those which are acute, result fatally. This seems to be true, also, of acute pericarditis following pneumonia or Bright's disease, but is not true of this complication of acute articular rheumatism.

The forms of tuberculosis as they are found in the pericardium are either of miliary form or cheesy masses. When effusion exists it is serous, bloody, or purulent. It may be moderate or considerable in amount. Whenever the condition has existed for some weeks, it is probable that the pericardial sac becomes softened and dilated and offers a very insufficient support to the heart. The clinical evidence of this softening and dilatation of the pericardial sac in disease is shown by its greater capacity to contain fluid. Experimentally, this capacity is limited to about 700 c.c. of liquid when forced into the sac.[2] In disease we know much greater quantities of fluid may be contained. Even when these larger amounts are present we can only recover them in part by paracentesis, owing, as will be shown later, to the position of the heart in the fluid. Soon the heart would show signs of dilatation, and this condition more surely and rapidly occurs if the heart walls are subjected to any increased strain.

In some instances of tuberculous pericarditis, as we know, adhesions with the chest wall have developed. These adhesions, if more than usually taxed, are apt, sooner or later, to be stretched and in some instances to give way. Under these circumstances the heart shows signs of insufficiency very soon.

As Sequira[3] points out, the dilatation of the pericardium is very important from the stand-point of ultimate prognosis, and this we can readily appreciate when we consider the immediate effects of hypertrophous dilatation where passive congestion of the viscera is more than likely to occur. Sequira's observations are based upon the history of 130 cases of acute pericarditis and observations of 1000 cases.

In occasional instances the pericarditis seems to be due to mere extension from adjacent parts in which tuberculous lesions clearly exist. Under these conditions the pericarditis, curious to say, may occasionally be simply inflammatory. This point is affirmed by Osler. Such instances have also been noted where the extension came from a case

[1] My second case.

[2] Chatin. Revue de Méd., June 10, 1900.

[3] British Medical Journal, June 17, 1900.

of non-tubercular pleuritis. Likewise they have been recognized as final complications of chronic tubercular states and as a result of terminal bactersemia. (Wells.)

In certain instances where the process in the pericardium is an acute one, tuberculosis has not had time to develop there, but later we should doubtless have discovered it if death from other organs affected with tuberculosis had not occurred. Tuberculous pericarditis heals through the formation of fibrous adhesions. In some forms, especially the caseous, the healing may be accompanied with calcification. The thickening of the sac wall may become very considerable. This is true of the parietal wall particularly. These cases are often accompanied with a deposit of numerous miliary tubercles. At the same time there is present more or less effusion, which may present different characters. Often it is distinctly bloody. Still this is not sufficient to determine the diagnosis, as it may take place in other conditions. Of the 11 cases found in literature by Sears,[1] 6 occurred in scurvy, 3 in rheumatism, 1 in goitre, 1 idiopathic, in an alcoholic subject.[2]

Bacilli may be found in this fluid, although sometimes it requires several careful examinations to reveal them.[3] Osler reports 1 case, quoted from Kast, in which tubercles have been found in the pericardial effusion. F. C. Shattuck's[4] second case is another. Where this examination has remained negative the bacilli are revealed solely by means of animal inoculations.[5]

The proportion of successful inoculations is considerable. It is of great value in fixing the positive diagnosis to be made. The drawback to it is the time it takes to develop tubercles.[6] It is in the exudate, as well as in layers of pericardium, that we find tubercle. When it occurs in pericardial layers it oftener affects the parietal one and disseminates to the left pleura. Serous effusion, when present, is frequently surrounded by fibrous exudation, which in places becomes adherent.

The myocardium may be affected with tubercular infiltration at the same time as the pericardium. The miliary form is relatively unimportant as compared with the caseous. The latter penetrates deeper and sometimes perforates the cardiac walls, and may surround itself with a fibrinous clot.

Formerly primary cases of tuberculous pericarditis were reported. To-day, thanks to a more advanced knowledge of pathology, this erroneous affirmation is rarely met with. One reason is because lesions

[1] Boston Medical and Surgical Journal, 1898, p. 293.

[2] Churtan. THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, 1892, p. 84; also, Michailoff, loc. cit., 1878, p. 278

[3] Report of my first case.

[4] Transactions of the Association of American Physicians, vol. xii. p. 194.

[5] This was true in my second case.

[6] About six weeks in guinea-pig.

formerly considered of doubtful nature are now recognized to be tuberculous. Hence, when such lesions are found elsewhere and by their structure are known to be of old date, we can readily appreciate that it is from them that the infection of the pericardium proceeds. In very many cases, without doubt, the infection is carried by the bloodvessels; in others the lymph channels are the evident way of transport.

Simple carrying, as it were, by extension of a tuberculous process through contact, although still admitted, is not so frequently allowed as heretofore. The ordinary development of tuberculous pericarditis is to run a subacute or chronic course. This course may be such an insidious one that for a long while the disease is latent and no obvious symptoms indicate its presence. Indeed, Osler reports only a single case in which, during life, "the diagnosis of tuberculous pericarditis was made with a reasonable degree of probability." If, however, there is no rheumatic history and tubercles are discovered elsewhere, with previous symptoms of pericarditis, we should think of the tuberculous form. The protracted course of the disease and the more marked irregularities of temperature may indicate its presence. Sometimes the symptoms occur, but are concealed by grave symptoms of other organs which are affected from general miliary tuberculosis as well as the pericardium. It is a fact also worthy of remark that, as a result of experimental researches about tuberculosis, while lungs, pleuræ, and mediastinal glands are usually attacked, it is a very infrequent circumstance to find the pericardium involved; indeed, it is doubtful if there be any well-authenticated cases of it. The involvement of the pericardium through the lymph channels and with transport of tubercle bacilli largely comes from the lungs, pleuræ, and peritoneum. This infection of cardiac lymphatics is doubtless carried on indirectly, so far as the former organs are concerned. Owing to the free anastomosis of the lymph vessels across the diaphragm, it is readily understood how a tuberculous peritonitis may cause directly the development of tuberculous pericarditis. Where the tuberculous pericarditis is of caseous form, brought from mediastinal glands, it is probable that later on this matter is carried to and produces secondary infection of the lungs and pleuræ.

In regard to the question of the frequency with which one layer of the pericardium is affected as compared with the other, this, it appears to me, is difficult of solution, despite the statement of Wells, and in any event of no practical moment.

What is affirmed with authority is that a large proportion of cases show tuberculous deposit in mediastinal lymph glands and pericardium at about the same time, and frequently this is true where no tuberculous deposit exists elsewhere. We are more likely to notice this dual condition where already the process has become somewhat a chronic one. Effusion into the pericardium is more likely to occur, it is stated,

where caseous masses exist on its surface than where we find the small gray tubercles.

Where the myocardium is affected the disease comes primarily, as a rule, from the pericardium. The muscle of the heart is, however, rarely thus diseased. This is especially true of the ventricle; the auricle is oftener invaded.

Tuberculous pericarditis may recover, it is stated. This is rare. In general, we may say it is not directly fatal, and death subsequently occurs from tuberculous deposit in some other important organ. At this time, that of the pericardium may have become quiescent. This, of course, occurs only in the relatively chronic forms. If it does, we may find fibrous nodules in the exudate or pericardial walls as the only direct evidence of a tuberculous lesion. It may be inferred, however, by considering the evident tuberculous condition of the mediastinal glands, and through the fact that this is the sole efficient cause of tuberculous pericarditis which can be brought to light.

The most important effects, clinically, are those which are seen upon the heart. In some instances there is no valvular lesion or structural defect of the heart muscle, and yet there is dyspnœa, cyanosis, and weakness of pulse—all pointing to cardiac distress. The effusion by its mere pressure seems to be the explanation of these symptoms, and its prompt removal is, therefore, the essential and urgent indication, so as to re-establish, as far as may be necessary, functional power. If this condition is allowed to remain, even though life may not be imminently imperilled, the heart soon shows the results of the external pressure against which it contends by becoming enlarged with hypertrophous dilatation, and by growing weaker progressively and constantly. Where adhesions exist with the thoracic walls, which is often true in these cases whenever they tend to chronicity, the duration of life is notably shortened. It is equally true, if not more so, where the two layers of the pericardium have also become adherent and the effusion has become resorbed or been removed by paracentesis. In these instances life may be measured by a few months. This is eminently true in pericarditis affecting children. Lee Dickinson[1] reports "one solitary case in which adhesion, certainly contracted in childhood, proved ultimately harmless." The late Dr. Sturges showed in these cases that acute carditis is present, usually of rheumatic origin. Peck[2] has ably described in several such cases a condition of "pericarditic pseudocirrhosis" resembling precisely the *mixed form of cirrhosis*[3] of the liver, which is due to a latent pericarditis. The differential diagnosis is based upon: (1) Absence of

[1] THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, 1895, p. 692.

[2] Ibid., 1896, p. 221.

[3] A case of pseudo-atrophic cirrhosis of the liver, secondary to adherent pericardium, is reported by Dr. R. H. Babcock, of Chicago, in the Medical News, December 14, 1901, p. 924.

etiological factor of cirrhosis; (2) a history of pericarditis supported with the evidences of it from physical signs.

We should not ignore the difficulty of explaining why pericardial adhesions are occasionally followed by such changes. Wells gives several good and sufficient reasons why tuberculous synechia is less to be feared than that which occurs in purely rheumatic cases. Among these may be regarded slowness of growth, no valvular defects, no toxæmia affecting heart muscle. Moreover, he states heart dilatation occurs in rheumatism at period of inflammation or later, when effusion is being absorbed.

In the latter instance, as I have already pointed out, the pericardium becomes dilated and softened, and thus fails to give the heart proper support. In addition to this, however, if the pericardium is attached to the chest walls it simply cannot follow the heart, owing to mechanical conditions. For this reason again, the heart yields more and more to internal pressure, and consequently becomes more and more dilated, weak, inefficient, and ultimately powerless.

In these cases we often find beneath a very thick pericardium a considerable growth of connective tissue, together with a deposit of fat in the superficial parts of the heart muscle.[1] In rare instances are we able to demonstrate the existence of gray tubercles in the myocardium. Where caseous deposits are found at the autopsy they are more important because they have penetrated the heart wall deeply, and in the event of perforation they serve to explain the transport of numerous bacilli in other organs and the signs of general miliary tuberculosis, which were easily recognized, even during life.

The usual termination of tuberculous pericarditis is death. This may be brought on directly by the recurrence of a large effusion, frequently hemorrhagic, which repeated tapping has failed to relieve. Of course, at times the adhesions which have formed to chest walls, lungs, and diaphragm seem greatly to shorten the duration of life; but these again may never occur, and the heart may simply float freely in the fluid which surrounds it more or less on all sides.[2] Often, as I have said, the fatal ending is immediately attributable not to the heart itself, but to the general miliary tuberculosis of different viscera with which the cardiac condition is associated.

Death may occur from an embolism, but this is extremely rare.[3] "Tuberculous pericarditis is generally unaccompanied by any symptoms referable to the heart, and is almost always an autopsy finding."[4] With this statement of Wells, corroborated by Osler,[5] judging by my two recorded cases, I should be inclined to differ.

[1] Second case reported by me.
[2] See my first case—pathological report.
[3] Case 8, reported by Wells.
[4] Loc. cit., p. 1458.
[5] Already cited.

For the cases which are slowly and insidiously developed there is little or no local treatment to be advocated. This is true of the cases which terminate in synechia and where the symptoms are frequently very obscure. The systolic retraction of the nipple in these instances is a deceptive sign, as more than once I have been able to observe. In this connection Lee Dickinson states we may have pulling in of lower ribs with systole, but adds that cases with this indication are seldom available. The most characteristic of all indications "are rapid progress of the case to the fatal end and the signal failure of all known means of relief in heart disease."[1]

Inasmuch as there is small effusion and no obvious inflammation, these two conditions may not require active interference. In those instances in which the onset of the disease is acute it is indicated at first to limit the amount of inflammation. Personally, I favor the local use of poultices or hot flannel stupes. To the former mustard may be added; the latter may be sprinkled with turpentine. Equal parts of soap liniment and turpentine applied for several hours on warm flannel are recommended. If cold be employed I much prefer Leiter's coil to an ice-bag. The latter is difficult to keep in place and causes distress from cold at times, which we cannot regulate easily.[2] A small quantity of morphine hypodermically may be called for to allay pain. In the cases that I have seen I have not thought the cautery or blisters were required in the beginning of the attack. Later, I am confident, repeated small fly-blisters may limit the amount of the exudate formed. It is also possible that an effusion already formed may thus be made to disappear, in part or wholly, and more rapidly than it otherwise would. Despite what has been said, it is far wiser in many cases not to attempt to influence the pericardial condition by any local applications. Whenever the effusion becomes considerable or excessive, paracentesis should be thought of. If the lips and fingers become cyanosed—if there is marked dyspnœa, and weak, frequent, irregular pulse—prompt withdrawal of fluid is necessary to preserve life. If before paracentesis is performed the exploring needle shows the presence of pus, it is more judicious, in many instances, to incise the sac freely and introduce a drainage-tube. Of course, if the condition of the patient is imminent, paracentesis may first be performed and subsequently the more radical operation.

The position of the heart with respect to pericardial effusions is frequently undetermined. In purulent fluids the heart is supported by or floats upon the fluid, and is carried directly against the chest walls. This has been proven experimentally. In fluids containing some blood,

[1] THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, 1896, p. 696.

[2] Of course, we can put a towel or flannel compress underneath.

or in pure serum, the heart is surrounded by fluid, as a rule, of which the larger quantity is in the lower and left lateral portion of the pericardial sac.

Whenever puncture of the heart is indicated, some hesitancy arises in performing the operation on account of the danger incident thereto. There is risk of wounding the mammary artery, of entering the left pleural cavity, of puncturing the liver, of wounding the peritoneum, or, indeed, of going through the diaphragm. Perhaps the latter is of no special moment, as it is the way by which entrance to the pericardium is occasionally suggested or taken by the surgeon in a radical operation.

The classical site for aspiration of the pericardium may be regarded as the left fifth interspace, near the sternal margin.[1] Other regions, however, have been tried more or less successfully, *i. e.*, beyond the left nipple and near the outer line of cardiac dulness; in the right fourth intercostal space; in the angle of the xiphoid cartilage and the margin of the left costal arch. The right interspace is specially indicated by Dr. Rotch, of Boston, in those cases where he has found dulness over this area.[2] Dr. F. C. Shattuck, in his able paper before the Association of American Physicians, Washington, 1897, has tried different points for aspiration of pericardium, with satisfactory and sterile results.

On one occasion where a small quantity of fluid was withdrawn, later the autopsy showed at least one pint of fluid in the sac. It may be inferred in such cases that the fluid thus discovered was produced during the agony or after death. It seems to me more probable that it was in the pericardial sac during life, but could not be aspirated, on account of the position of the heart and the wrong point of puncture.

In this connection I am glad to be able to refer to a recent able article by Dr. O. Damsch,[3] which settles definitely, it may be, most points hitherto questionable about the position of the heart, that of the effusions, and the point where we should always try paracentesis. Dr. Damsch made injections experimentally into the pericardium, the subject being in the upright position, for the purpose of determining the position assumed by the pericardial exudates. *Small amounts*, he found, collect in the lower and antero-lateral portions of the pericardium, causing approximation of the right anterior portion of the pericardium to the chest wall. The heart, when of *normal size*, was always found pressed against the posterior portion of the pericardium, the fluid occupying the

[1] Roberts states (Trans. Surg. Assoc.) that this point of election "will not assure safety to the pleura."

[2] The clinical conclusion from Damsch's experiments was that "first sign of pericardial effusion would be area of dulness in heart-liver angle, as taught by Rotch." (Loc. cit.)

[3] Gould's Year-book, 1901, pp. 178–179.

anterior portion. In cases in which the heart was hypertrophied it was pressed *upward* and *anteriorly*. Its increased size, according to Damsch, causes it to fill the whole space between the anterior and posterior chest walls, and, therefore, since the fluid collects in the lower part (pericardium), the heart must be pressed upward. "From his experiments he decides that the best position *for puncture* is well down toward the lower part of the pericardium." He also decides that puncture in the fifth or sixth intercostal space (left) next to the sternum, directing the trocar somewhat inward, is the safest method and location of paracentesis. Thus performed there is no danger of wounding either heart or pleura. If the heart is normal the fluid is in front of it and at lower part of pericardium; if the heart is *enlarged*, which it usually is, it is floated *upward* and *out of danger*.

Aspiration of the pericardium relieves, without doubt, for a while imminent symptoms, and, as an operation of urgency, should be employed unquestionably. When we come to consider it as a curative means it is of less value. I have seen the fluid recur several times after it has been removed, and that, too, in a relatively short period. This statement is true of instances in which the pericarditis, either at that time or subsequently, was known to be tuberculous. One is thus led to ask whether in these instances it is not preferable to perform a radical operation with proper surgical technique and thorough drainage of the pericardium. In purulent cases the general consensus of good surgical judgment is to that effect. In tubercular cases where the effusion is not purulent it may be also a wiser procedure than simple puncture, because through the open wound the finger may be introduced, and large masses of fibrin extracted. These masses, if allowed to remain *in situ*, inevitably delay cure by allowing fluid to re-form rapidly. After a reproduction of fluid on one or several occasions, adhesive pericarditis may and does develop, and, sooner or later, we have to do with a seriously crippled heart. There might be a chance of obviating this by means of the canula left in place and the use through it of some form of alterative injection. Rendu[1] reports such a case of cured tuberculous pericarditis. The modifying injecting fluid employed by Rendu was a solution of pure camphorated naphthol.

What is true in cases where effusion has been withdrawn as regards some of the results to heart fibre is true where we leave the fluid in the pericardial sac and do not attempt to remove it. By and by underneath the thickened layer there comes a large layer of fat. This fat finally penetrates the heart wall between the muscular fibres, and, in connection with a deposit also of cellular tissue, leads to fatty degen-

[1] Journal of the American Medical Association, 1901, p. 1432. Also, Bull. de la Soc. des Hôpitaux de Paris, March 21, 1901.

eration of the heart structure, and later, perhaps, to combined fibroid changes.

As regards serous effusions, even though large in amount, such as we meet with as a complication, especially of acute articular rheumatism and occasionally in nephritis, these rarely require puncture, in my judgment. Whenever the indication arises, unless the condition be very imminent, I am of the opinion that one or a succession of fly-blisters over or near the heart will accomplish all that is urgently required. It is not essential, moreover, that much fluid be removed from the pericardium in these cases so as to promote absorption; a small quantity is sufficient. The proof of this is that often after aspiration of the pericardium, where very little fluid has been actually removed, a notably beneficial effect quickly follows. The same thing results from a severe counter-irritant or revulsive. How this acts (blister)[1] I am not quite sure. Evidently there is no immediate vascular connection between the skin in the præcordial region and the heart itself, and for this reason it would seem as though the blister would do as much good were it placed over a region far removed. Certainly, if mere reflex action comes into play it is possible. And yet, somehow or other, I am a believer in its good effects applied over the præcordium, and I do know that revulsion, irritation, or heat locally over the heart is of great practical value in adding to its power. I can readily conclude, therefore, that wherever effusion in large amount is partly passive, increased heart action may be remedial in a very distinct and rapid manner.

With respect to the operation of paracentesis *versus* the use of counter-irritation in those cases where the effusion is limited and probably serous, we should always have in view the possibility of change to a purulent effusion caused by the little operation itself, especially if performed with the ordinary trocar and canula. With proper aseptic precautions and the use of the aspirator, this to-day may be regarded as a negligible quantity. Moreover, it is known that but one case has resulted fatally following the puncture. "With this exception all the patients were greatly relieved by the removal even of a small amount of fluid, and many recovered completely who probably would have died if the operation had not been performed."[2]

In purely purulent effusions it is now generally admitted that surgery with open wound, with or without drainage, should alone be considered. Porter's case[3] and others still prove this. Only lately, for example, H. Lilienthal has had a successful radical operation in a

[1] Dr. Shattuck never uses blisters. Drs. Tyson and Rotch would not let them go.

[2] THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, 1897, p. 458.

[3] The only case ever treated by incision in Massachusetts General Hospital (F. C. S.). Boston Medical and Surgical Journal, May 6, 1897, p. 438.

case of purulent pericarditis. Here aspiration had proved insufficient. In Lilienthal's case a portion of the fifth left costal cartilage was resected close to the sternum under local anæsthesia. Forty ounces of fluid were removed from the pericardial sac.[1]

In another case, reported by Ogle and Allingham, the pericardium was opened, a large quantity of pus removed, and the pericardium cleansed, without interference with the action of the heart and with decided benefit to the patient. It was shown in this instance that the heart can be handled without harm. It is therefore advisable to treat these cases precisely as we would an empyema. Indeed, the operation is more indicated than that of empyema, because the walls of the cavity are better able to contract and finally lead to complete obliteration. We know the outcome in empyema, where, to reach the best obtainable result, portions of several ribs must often be resected. Even then we have to deplore many incomplete successes.

Finally, in the operation by opening and drainage we have really the only legitimate hope of entire recovery. No one has insisted upon this operation more strenuously than Dr. J. B. Roberts since 1876. In a late paper he reiterates his findings. Very properly, he says, "the diagnosis of the purulent character of the effusion was only determined by exploratory puncture."[2] And "this should be done at the upper part of the left xiphoid fossa close to the top of the angle between the seventh cartilage and the xiphoid cartilage."[3]

"The prognosis is good," says Dr. Roberts, "in pericardotomy for pyopericardium. In a table of 26 collected cases 10 recovered and 16 deaths were shown. This gave a percentage of recovery of 38.4. Of the fatal cases at least 9 were septic, and all the others who died had complicated lesions such as pleuritis, or pulmonary, cardiac or renal lesions."[4]

"The results obtained by incision and drainage in tubercular peritonitis suggest that drainage in tuberculous pericarditis may lead to a permanent cure. The ease with which the pericardium can be irrigated with solutions of iodoform would seemingly add to this probability of success."[5]

After analyzing different cases, Roberts writes: "These observations and other reported cases not here mentioned have almost convinced me that incision is better than aspiration even in cases not supposed to be purulent. It establishes diagnosis in dubious cases, avoids cardiac injury, saves the pleura from puncture, affords complete evacuation of effusion, permits extraction of thick pus and membranous lymph, and gives opportunity for disinfection of the sac when that is necessary."[6]

[1] New York Medical Record, November 25, 1900.
[2] Boston Medical and Surgical Journal, May 27, 1897, p. 522.
[3] Loc. cit.
[4] Loc. cit.
[5] Transactions of the American Surgical Association, 1897, p. 108.
[6] Loc. cit.

Porter cites one successful case of incision in serous pericarditis where puncture failed to relieve.[1]

Personally, so far as tuberculous cases are concerned, I agree with Dr. Roberts. Ordinarily, in cases of simple serous effusion of other provenance I do not believe incision is called for, and if any operative interference is required I still prefer paracentesis. If irrigation be employed as an adjunct in incision the outflow of fluid must be unimpeded, or death may rapidly result from it.

In regard to the technique, it is not necessary to say more than to point out that the best operation is the one usually which permits best drainage in a given case. In one instance it may indicate resection of the fourth or fifth rib on the left side; in another the pericardium should be opened from below and through the insertion of the diaphragm near the central tendon.

It should be remembered, in my judgment, that the question of radical operation for pericarditis with effusion is different in one very important particular from that of pleurisy with effusion. There are two lungs; there is only one heart. A patient may do fairly well for a long time with pleuritic adhesions, a retracted chest wall, and an atelectatic and fibroid lung. No patient will continue long to be in any degree comfortable or active who has adhesive pericarditis as a sequela of large and long-continued effusion, with the pathological changes of heart walls which invariably follow sooner or later.

To those who have had small clinical experience with these cases and who may be led to believe that the liability of heart puncture is slight, I would point out that the anatomical relations of the pericardial sac, despite Dr. Damsch's researches with the chest walls and left pleura, in many instances are very perplexing and variable. As to the differential diagnosis of pericardial effusion with a heart merely enlarged, while this is often very simple and requires no great medical acumen, there are occasions when the most careful use of physical methods of exploration will leave one in a state of great uncertainty. Again, I have had to do with cases where I was confident there was a large effusion and no risk in introducing a small trocar connected with the aspirator. Unfortunately my diagnosis was incorrect, manifestly on one occasion, and instead of withdrawing fluid from the pericardium my aspirating needle penetrated the heart wall. This was obvious by reason of the fixed position, and special movements transmitted to the canula when the trocar was withdrawn. In this instance no great or immediate harm resulted. Still, it is an accident to be avoided, as far as possible, by great care and attention.

Orphüls reports a case where, at the autopsy, the end of a trocar

[1] Transactions of the American Surgical Association, vol. xv.

needle was found in the scar tissue at the upper portion of the interventricular septum. This needle probably broke off in an exploration or in a previous operation of paracentesis.[1]

Loison[2] affirms, also, that in wounds of the heart and pericardium the "prognosis is not always grave." This judgment is strengthened by the statistics collected both by Fischer and himself. On the other hand, Rotch has "known of a case where pricking the heart with an aspirator needle has caused sudden death," and Janeway one where the aspirating needle tore the heart, causing death.

Formerly, so as to avoid just such mishaps, I had constructed for myself a modified Roberts canula.[3] This is a very good instrument when kept in proper order. It is a little complicated, however, and requires to be looked after. All that precedes acquires additional interest, if we recognize, as many do, that the ordinary medicinal remedies as applied to the treatment of pericarditis with effusion (especially the tuberculous form) have very little value.

I am not aware, once pericarditis has become developed, that any remedy given internally abridges its duration or changes its course very perceptibly. I acknowledge, of course, in a few instances, that the heart needs special stimulation in view of the failure that may come on suddenly or by degrees. The alkaline treatment may prove very useful in giving strength to cardiac contraction—more, indeed, than the use of digitalis. This would be in accord with the experiments of Gaskell.[4] I also know that in a few—a very few sthenic cases—aconite may be indicated for a short time to lower blood tension and decrease the rapidity of the pulse; but that is about all there is to do in the acute stage by way of the mouth. Locally, as I have already pointed out, the ice-bag or poultices, blood-letting (leeches and cups), are useful where there is pain or great increase of heart action. Beyond some degree of soothing or quieting thus produced, we should not count upon a great return.

The prophylactic measures to be employed have to do solely, it seems to me, with the efficient causes of tuberculous pericarditis which prevail, be it possibly pleurisy, pneumonia, sepsis of some sort, or mere exposure, fatigue, or debauch.

As we know already, tuberculous pericarditis may show itself when we have had little or no suspicion of its presence. It may also be ushered in with so few obvious symptoms or signs, local or general, that except in an accidental way it is not discovered during life. There are many examples, indeed, where the presence of the disease

[1] British Medical Journal, January 27, 1900.
[2] The American Journal of the Medical Sciences, 1900, p. 218.
[3] Medical Record, March 29, 1884, p. 361.
[4] The American Journal of the Medical Sciences, 1896, p. 696.

was ignored during life and only ultimately revealed by the findings at the autopsy.

Appended is an abstract of the history of my second case:

History of case of tuberculous pericarditis (No. 2). B. F., married, a hod-carrier, born in the United States, aged thirty-eight years, was admitted to St. Luke's Hospital under my care, March 19, 1901. Family and personal history negative, save that he was a somewhat excessive drinker of beer and whiskey. Present illness began four months ago, after a debauch, with pain in his right side. No cough, chills, or vomiting. The pain in the side lasted a month, when he began to cough, expectorated blood-stained mucus, had some fever, with afternoon exacerbations, and became weaker. Two weeks ago pain in the præcordial region, with palpitations, developed; also at times dyspnœa. No swelling of the feet.

Physical examination shows marked increase of cardiac dulness, rapid heart action, and a high-pitched systolic murmur, heard between the nipple (left) line and sternum. Thoracentesis gave serous fluid in right pleural cavity. Temperature, 99.3° F.; pulse, 100; respiration, 49. *Urine*, acid, 1020; no sugar, no albumin, few leucocytes. No tubercle in sputum.

X-ray examination shows shadow corresponding to line of cardiac percussion dulness.

Microscopical examination of blood negative; also examination of eyes negative.

April 25th. Guinea-pig inoculated with fluid from right pleura. On May 19th tubercle found in cheesy pus from enlarged lumbar glands of guinea-pig.

May 26th. Patient paralyzed on right side. Soon became comatose and died the same day. During sojourn in the hospital the patient was feverish, with pronounced irregular rise in the afternoons.

Autopsy, made by Dr. N. E. Ditman, resident pathologist, showed much thickened pericardium; sac contained eight ounces of yellow, turbid fluid. Heart enlarged, muscle pale, and covered by a layer of subpericardial fat; valves normal, save a slight atheroma of one flap of mitral. Lungs, liver, spleen, meninges, and peritoneum showed disseminated miliary tubercles.

Microscopical examination showed cheesy degeneration and numerous giant cells throughout the pericardium. In the layer of fat over the heart and beneath the pericardium were numerous small masses of small round cells, and in each mass giant cells were present. The heart muscle, superficially, was infiltrated with fat. More deeply there was a moderate small round-cell infiltration between the muscle bundles, and in places the latter are separated by connective tissue; connective tissue of bloodvessel walls increased in amount.

NOTE.—Since writing my paper a very interesting case of tuberculous pericarditis with effusion has been reported by Dr. F. R. Sabin[1] from Prof. Osler's clinic. "The points of interest are: (1) the great value of repeated tappings in serous effusions; (2) the finding of tubercle bacilli in the pericardial exudate, and (3) the high percentage of mononuclear forms in a tuberculous exudate."

[1] American Medicine, March 8, 1902.

A CASE OF AORTIC INSUFFICIENCY, WITH PERICARDITIS, PLEURISY, AND MEDIASTINITIS.[1]

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The following report of an isolated case would seem justified by reason of its unusual character, of the prominence of the physical signs, of the disparity between these and the remaining symptoms, of the etiological relations, and of the diagnostic considerations.

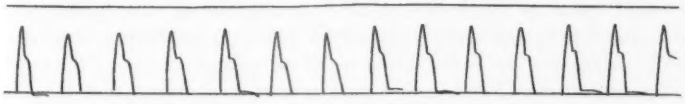
A man, aged forty years, by occupation a printer, presented himself at the Polyclinic Hospital, complaining since four months of constant pain throughout the entire chest and back, worse at night and also during inspiration. There was, besides, palpitation of the heart, slight cough with mucous expectoration, and some dyspnœa. There had never been hæmoptysis. The appetite was good, the bowels regular. Sleep was poor, and the frequency of micturition was increased. The lower extremities were slightly œdematous. The man was pallid, and he had lost thirty-six pounds in weight during the period of four months. He presented an appearance of distress.

The left side of the chest was comparatively prominent anteriorly. The cardiac impulse was visible in the sixth interspace on the left in the nipple line, but pulsation could be felt also in the seventh interspace out to the anterior axillary line and at the ensiform cartilage and for some distance on either side. Systolic retraction of the intercostal spaces took place over a large extent of the inferior portion of the left chest, anteriorly and posteriorly, and some degree of retraction appeared to be present also on the right side inferiorly. A thrill was palpable over the body of the heart and apparently a separate and more marked thrill in the aortic area, and also a thrill intermediate in intensity to the right of the sternum in the third and fourth intercostal spaces. The thrill was in each instance diastolic in time. The area of cardiac dulness was increased, particularly downward and to the left.

On auscultation attention was first attracted by a rough though musical murmur, audible throughout the præcordium, but heard with greatest intensity in the aortic area. It could be detected, even through the air, at a short distance from the chest, and it was heard also in the axilla and in the back, gradually losing its musical quality, which, however, became again appreciable along the left of the vertebral column. In this situation the murmur was most pronounced at the level of the spine of the scapula. This sound was followed or preceded by a dull, booming sound, synchronous with the impulse of the heart and the radial pulse. Over the vessels of the neck the transmitted murmur and a dull thud were heard in succession. At the base of the

[1] Report read and patient demonstrated before the Section on General Medicine of the College of Physicians of Philadelphia, January 13, 1902.

heart creaking sounds were audible with the cardiac sounds, being intensified by deep inspiration, and fine crackling was brought out when the patient inclined the body backward. These signs were less pronounced when the body was inclined forward. The radial pulse exhibited a water-hammer character, and this is well shown in the accompanying sphygmogram.



The right radial did not pursue its normal course, at the wrist passing on the outer side of the radius. A systolic thrill was generated by pressure over the subclavian arteries.

In the erect posture the line of percussion dulness to the right of the sternum pursued a zigzag course obliquely downward and outward across the sixth, seventh, eighth, and ninth ribs. In the middle line the lower limit of dulness was 9.5 cm. below the ensiform cartilage, and in the right nipple line 5 cm. below the costal margin. In the recumbent posture both boundaries descended from 3 to 6 cm., and a sense of resistance was appreciable along the lower border. Percussion over the area of dulness below the costal margin was attended with tenderness.

In the epigastrium, below and to the right of the ensiform cartilage, was a scar left by a stab wound inflicted three years previously. The pupils were practically equal, although the left may have been slightly the larger.

The patient stated that he had had scarlet fever and smallpox as a child and influenza at the age of thirty years. He denied venereal infection. He drank several cups of tea or coffee daily, but no alcohol. The urine was free from albumin and sugar.

There was some doubt at first as to whether the loud musical murmur heard over the heart was systolic or diastolic. Its predominance in duration and intensity over the other sound, which exhibited a dull, muscular character, suggested the possibility of its being systolic in time; but its asynchronousness with the impulse of the heart, with the radial pulse, and with the thrill appreciable on palpation of the subclavian arteries, together with the sounds heard over the vessels of the neck, convinced me that the murmur was diastolic.

Some difficulty was experienced also in providing a satisfactory explanation for the thrill palpable in three situations with varying intensity. The creaking sounds at the base of the heart suggested the presence of adhesions resulting from previous pericarditis and pleurisy, with involvement of the mediastinal structures, and it was thought that the thrill palpable in the same situation might be due to circulatory disturbances in an atheromatous aortic arch possibly dilated at its origin. The thrill over the body of the heart may have been due to the same cause or to

vibrations in the anterior mitral leaflet generated by the current of blood returned from the aorta into the ventricle. The systolic retraction in the lower interspaces on both sides of the chest, but particularly on the left side, seemed to confirm the view as to the presence of pleuropericardial adhesions.

The liver appeared to be movable, in the recumbent posture rotating forward upon its transverse axis. The presence in the epigastrium of a scar left by a previous stab wound raised the possibility of a traumatic origin for the lesions; but as these seemed to be multiple and rather widely distributed, and in part remote in situation, such an etiological connection could be excluded and an antecedent infectious process made the responsible factor. It will be noted that there is a history of scarlet fever, smallpox, and influenza, but none of rheumatism; nor is there anything in the patient's occupation to which the lesions present could reasonably be attributed. It is now practically established that inflammation of the endocardium and of serous membranes and even of synovial membranes may attend any infectious process; and it may occur, I am sure, in the absence of any obvious primary localization, as a result of so-called cryptogenetic invasion. Acute rheumatism has long been considered by far the most common cause of chronic valvular disease of the heart; and while this view is sustained by the results of critical inquiry,[1] inasmuch as rheumatism has been shown to be a more important etiological factor than any other infectious process, the disease named has been found to be less significant in this connection than all other causative factors combined. Further, I am inclined to the belief that under the clinical designation rheumatism are included many forms of arthritis, involving one or more joints, but that among these there is one with a definite clinical course and probably dependent upon a specific micro-organism—possibly that described by Poynton and Paine;[2] and for this the designation acute rheumatism or rheumatic fever should be reserved, while the others are to be classed among articular infections of diverse origin.

Murmurs audible at a distance from the chest are not common, but by one of those coincidences that are not rare in medicine a patient presenting a murmur like that in the case here recorded was exhibited by Dr. Alfred Meyer at a meeting of the Section of Medicine of the New York Academy of Medicine.[3] In this case also the murmur was of aortic origin, diastolic in time and musical in quality. It could be heard at a distance of from two to six inches from the chest. It was thought probable that the aortic orifice was enlarged or the root of the aorta dilated, resulting in relative insufficiency of the aortic valve. To

[1] Worobjew. Deutsches Archiv für klinische Medicin, Bd. lxix., H. 5 u. 6, p. 466.
[2] Lancet, September 22 and 29, 1900, and May 4, 1901.
[3] Medical Record, February 8, 1902, p. 237.

produce a musical murmur it was believed necessary for the surfaces over which the blood stream passed to be quite smooth. Dr. Meyer estimates the frequency of murmurs audible at a distance from the chest as perhaps 1 in 300 cases of heart disease.

NOTE.—At a meeting of the Section following that before which the case here reported was presented Dr. H. A. Hare exhibited a case of aortic insufficiency with a diastolic musical distance murmur.

THE FLUORESCENCE OF QUININE AND OTHER REMEDIES IN THE CURE OF MALARIAL FEVER.

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IN a recent paper* it was maintained that the malarial parasite would not sporulate in the dark; that the light it obtained in the blood was necessarily *red;* and, following the demonstrations of Harrington and Leaming,[1] that *amœba proteus* streams in the presence of *red* light and ceases to stream in *violet* light, it was assumed that the same may be true of the *malarial* amœba; hence it was suggested that the curative action of quinine might be due to its fluorescence, producing violet rays of light in the blood. Evidence in support of this view will now be presented

First, it may be noted that two other vegetable products possessing blue fluorescence in a remarkable degree have long been known as effective remedies for intermittent fever, viz., esculine and fraxine (or fraxinine).

As to the efficacy of esculine former records furnish abundant testimony. Notably, Monveneux[2] reports in detail twenty-eight cases successfully treated, a report the reliability of which is accentuated by the author adding ten other cases which esculine failed to cure, but which were promptly relieved by quinine.

An article in the *French Dictionary of Medical Science*[3] refers to the experiments of MM. Mouchon, Durand de Lunel, Diday, Vernay, and Monveneux, as demonstrating that esculine is comparable to quinine as an antiperiodic. The bibliography at the end of this article contains twenty-three references to esculine, dating from 1720 to 1858.

I find esculine presents, in solution, a far more brilliant blue fluorescence than any salt of quinia or cinchona. Its fluorescence is, how-

* THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, February, 1902.

ever, immediately destroyed by dilute sulphuric acid, but promptly reappears by adding a few drops of aqua ammoniæ to the solution.*

Fraxine—the other fluorescent substance named—is made from the bark of *Fraxinus excelsior*, the common ash tree of Europe. This was often given successfully for intermittent fever before the discovery of quinine, and later, one writer who reports cases cured by it, in which quinine had previously failed (?), was so convinced of its efficacy that he surnamed it *quinquina d'Europe*.[4]

The tincture and other preparations of *iodine* have been used successfully for intermittent fever for a long time. The literature on this subject is extensive. Sircar[5] gives seven successful cases, and quotes Grinnell[6] to the effect that "one hundred and forty cases were treated with the iodine, and the results were fully equal to those treated with the sulphate of quinine. The remedy seemed to act almost as by magic," etc.

Now, while iodine is *not* fluorescent, and cannot, therefore, act (as suggested for quinine) by accentuating violet rays, yet in the body it can scarcely escape coming in contact with starch and forming the *blue or violet iodide of starch*, which is all the more likely to occur from the iodine being usually given *after meals*, to avoid its irritating effect on an empty stomach. Thus the curative influence of tincture of iodine would seem to fall in line with that of Prussian and methylene blues. One writer, Entrikon,[7] prescribed the *iodide of starch* itself, but finally settled upon the compound tincture of iodine as the best of several preparations.

While the antiperiodic effect of the fluorescent substances esculine and fraxine favor the idea that fluorescence may be the curative property in quinine, the proof is insufficient. We need direct experiments showing that quinine actually produces fluorescence in the body, and that coincidently the symptoms and phenomena of malarial fever disappear.

Exactly these results were actually obtained more than thirty years ago (1868) by the experiments of Drs. Edward Rhoads and William Pepper, of Philadelphia. These experiments, so long buried in oblivion apparently, were brought about in the following manner: In 1866, Henry Bence Jones,[8] experimenting on the rapidity with which medicinal substances pass into and out of the body, was induced to use quinine for this purpose on account of the extremely minute quantity of this substance (1 grain in 1,000,800 parts—nearly 117 litres of water) that could be recognized by its fluorescence. To his surprise, he found that fluorescence existed in the blood and most of the tissues

* I obtained the drug from Merck & Co., of New York, who, in their "Index" for 1896, p. 93, describe it as an "antiperiodic. Uses: *Instead of quinine for intermittent fever.*" They inform me that little is sold, probably from its high price—three cents per grain.

of man and animals in those who had *not* taken quinine, but it was increased in those who *had* taken it. Without following him in detail, Jones obtained the result—interesting to us now—of discovering a substance in the tissues of guinea-pigs and man which possessed *all* (*italics* his) the chemical and optical properties of quinine, including fluorescence. He called it *animal quinoidine*. Early in his paper Jones remarks: "No imagination could have anticipated that this line of research into the rate and passage of substances into and out of the textures would lead to the supposition that man and all animals possess, in every part of the body, the most characteristic peculiarity of the bark of the cinchona trees of Peru;" and later in his paper he says: "Assume that a substance like quinine exists during health in the textures, can its rapid destruction and removal through the action of the marsh miasm* give rise to ague?"

Following Jones, Drs. Rhoads and Pepper[9] endeavored to determine "whether there might not be, as an attendant upon the pathological processes in malarial disease, a rapid and marked diminution in the amount of 'animal quinoidine' naturally existing in the tissues."

They first repeated the experiments of Jones and corroborated his results, and then proceeded to test the blood of malarial patients, with the result of finding its *fluorescence below the normal standard*. Altogether they give twelve cases, amply described and tabulated. They obtained blood by cupping over the spleen, and the degree of fluorescence was determined by comparison with the fluorescence of standard solutions of quinine of known strength—a given number of grains in 100 litres of distilled water. Thus a fluorescence of 3 would equal that of a quinine solution having 3 grains of quinine in 100 litres of water; a fluorescence of 6 would equal that of 6 grains in 100 litres, etc.

Their twelve cases may be epitomized with extreme brevity, as follows: Case I. Healthy woman. Fractured bones. Blood-test gave fluorescence of 3. Case II. Tertian ague; fluorescence, 1½. Case III. Marked intermittent; fluorescence, 1. Case IV. Marked intermittent; fluorescence, ½. Case V. Tertian; fluorescence, ½. Case VI. Quotidian; fluorescence, ¾. Case VII. Quotidian and tertian; fluorescence, ¾. Case VII. Quotidian and tertian; fluorescence, ¾. Case VIII. Tertian; fluorescence, ¾.

These cases show a fluorescence of 3 in the normal woman, and of less than 1 in five of the seven cases of fever, the other 2 being severally 1 and 1½. In these seven cases no quinine was given, and care was taken to ascertain that none *had* been given for some days before the examination.

* This was thirty-four years before Laveran discovered the malarial parasite in 1880, and before the part played by the mosquito in malarial disease was recognized in 1883.

Then follow 2 cases showing increase of fluorescence and consequent cure by sulphate of cinchona.*

Case IX. Quotidian; fifteen months' duration; spleen enlarged. Fluorescence: "*none* could he discovered, and it was doubtful if any existed." After fourteen days under cinchona sulphate no recurrence. Much improved; fluorescence, 1¼.

Case X. Quotidian for nine days following previous irregular symptoms. Fluorescence, ¾. After six days, cinchona sulphate 20 grains daily; fluorescence, 3½; no recurrence of chill.

Next come two fatal cases. One (XI.) was a quotidian of four weeks' duration. Last two paroxysms congestive; the final one at 11 A.M., death at 2 P.M. Had taken 20 grains of cinchona sulphate two days before death, and one or more doses of 15 grains each on the day of decease. Post-mortem examination revealed fluorescence of 2½ in blood of spleen and 2½ in blood of liver.

Case XII. Chronic malarial cachexia; ten months' duration; general dropsy three months; improved under cinchona and Basham's mixture, then typhoid fever, and death on ninth day of that disease. Took *large doses* of cinchona for *fifty-four days* preceding demise. Fluorescence in blood of spleen, 6, and of liver, 8.

At the conclusion of their paper the authors remark that their observations "indicate, by the uniformity of the results, a close connection between the diminution of 'animal quinoidine' and malarial disease."

In 1875 Mills,[10] of Philadelphia, suggested that fluorescence may afford an explanation of cinchonism. Commenting on the experiments of Jones, Rhoads, and Pepper, he says it has been proved that animal fluorescence is increased by quinine; that it "is decreased below a normal standard in malarial affections, and that it rises in the scale *pari passu* with the giving of the cinchona preparations and the improvement in the symptoms of the diseases."

Thus, then, it is the peculiar relations of the cinchona preparations *with light* that give a clue to the explanation of their curative effect. Possibly the same may be said of *all* assimilable substances that fluoresce a *violet* or *blue* color. Some substances have a green, orange, or red fluorescence; these we should not expect to have any curative influence in malarial disease.

It remains to explain the cases in which quinine *fails* to cure—exceptions that seem to prove the rule that the malarial organism will not sporulate in the dark, and, further, that *in* the dark quinine (necessarily) cannot kill the parasite with fluorescent *light*.

In these cases the febrile paroxysm is not produced by the usual ter-

* *Cinchona* sulphate was used instead of quinine. Authors do not state why. Probably the quinine salt may have been too expensive for hospital use in those days.

tian or quartan parasite, but by the "malignant" crescentic form of which Manson[11] gives three varieties, viz.: 1, æstivo-autumnal; 2, malignant quotidian; 3, malignant tertian. He calls all of these crescentic forms "malignant infection," and says "the malignant parasites *alone* form crescent bodies" (p. 65); that quinine "has apparently no influence on these bodies" (p. 66); they "may be found for days after the patient is cinchonized" (p. 44); or, "after full doses of the drug continued for a fortnight" (p. 183). The malignant parasite does *not* cause fever paroxysms, but is usually associated with marked cachexia" (p. 66); all of which is explicable by the further facts that "these crescent parasites are not generally found in the *peripheral* circulation" (pp. 15, 65, and 85), where they can get *light*, but *are* found in the spleen, liver, bone-marrow, and brain, than which no *darker* recesses of the body can be imagined, and consequently where the fluorescent property of quinine *must* be impotent. When they *do* appear in the peripheral circulation "it is a sure sign that a paroxysm of fever is impending" (p. 69); that is to say, having come out of their dark recesses into the red light of the peripheral blood, sporulation occurs, and with it the usual ague paroxysms. These quinine may arrest, but it cannot act upon parasites in the dark.

Possibly the malignant parasites are sickly, degenerate, or famine-stricken individuals, from the man's blood being overstocked or anæmic. The corpuscles containing them are *not enlarged* like those containing benign tertian parasites; the latter may be sometimes nearly twice the diameter (Manson, p. 62) of healthy corpuscles.

A normal capillary will just admit one nornal corpuscle to pass, and while both are elastic, and the skin capillaries among the largest in the body, it is conceivable that the enlarged corpuscles with benign tertian parasites *become arrested* in the skin, on account of their size, and so remain until light causes them to break up by sporulation; on the other hand, the smaller corpuscles with crescent parasites are *not* arrested in the skin capillaries so as to be continuously exposed to light, but pass on and become arrested by smaller capillaries in the brain or elsewhere. Some of them may eventually get light enough to manage sporulation, at odd times, or continuously, but not a sufficient number sporulate *simultaneously* to generate a fever paroxysm.

In a normal case of typical tertian ague the successive events that occur during the three stages of chill, fever, and sweat are as follows: Previous to the chill a group of corpuscles lies arrested in the peripheral capillaries, their parasites exposed to sunlight preparatory to sporulation. With the sporulation is the *chill*, by which the skin arterioles are violently contracted and emptied of blood; hence, pallor and coldness of the surface; and, as if to assist in the dislodgement of the infected corpuscles and their complete disintegration, the whole fabric

of the man's body vibrates with a "shaking chill." During the *fever* the arterioles dilate again, even beyond the normal limit; an actual congestion of the skin occurs; hence its redness and heat, during which a new crop of infected corpuscles enters the peripheral capillaries. During the *sweat* a deluge of water exudes from the distended cutaneous bloodvessels, causing them to contract, close up, and shut down upon the new group of infected corpuscles, which, thus arrested, so remain until forty-eight hours of sunlight secures in turn their sporulation and the recurrence of another paroxysm. Thus a typical tertian paroxysm might be regarded as a *functional disease* (or process) *of the skin*, during which the human organism is operating, according to nature's laws, in the interest of the parasite to secure perpetuation of its species. If the process were allowed to run its natural course without interruption (without clothing, quinine, etc.) the human individuals, or their race, in the course of many generations, get their compensation by becoming black from malarial melanosis, with the same immunity that now belongs to dark-skinned peoples.

Thus regarding the malarial process as *naturalists* instead of *medical practitioners*, this new point of view presents confirmatory evidence of the rôle played by sunlight in producing the observed phenomena.

Finally, the idea that succession paroxysms of fever are produced by sporulation of successive groups of those parasites *only* whose domiciliary blood-corpuscles have become sufficiently enlarged to cause their arrest in the cutaneous capillaries is, I am aware, at variance with the generally recognized theory of Golgi that the paroxysms are produced by successive *generations* of parasites, each fit corresponding to the ripening, sporulation, and setting free of a *new brood*.[12] My idea is that only such a *part* of any generation, the blood-corpuscles of which have become large enough to get arrested in the peripheral circulation, sporulate at any one paroxysm. The others must take their turn, waiting until the corpuscles they inhabit have become increased in size sufficiently to get arrested in the skin, where sunlight may be obtained to secure their sporulation also.

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A STUDY OF HYPERPLASIA OF THE PHARYNGEAL LYMPHOID TISSUE (ADENOIDS), WITH ESPECIAL REFERENCE TO PRIMARY TUBERCULOSIS OF THE PHARYNGEAL TONSIL.

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Introduction. The most important recent literature on the pharyngeal tonsil relates to tuberculosis of this tissue. While many of the newer investigations have thrown considerable light on the morphological and clinical aspects of the lesion, numerous points still remain to be settled. Perhaps one of the most interesting of these at present is the frequency with which this lesion occurs, and whether or not the lesion remains focal or may become disseminate. Thus far the results of study as to the frequency of the lesion permit of widely different interpretations; and in order to throw further light on this point we have restudied the question in a systematic manner, and have, in the course of our investigations, incidentally touched upon certain questions related to the bacterial infection and general pathology of adenoids.

The Normal Tonsil. Considered either from the anatomical or physiological view-points, the various lymphoid tissues of Waldeyer's ring present fundamental features in common. Their morphology and function have best been studied in the faucial tonsil; and only very recently, and to a much less extent, have similar observations been made on the pharyngeal lymphoid tissue.

The tonsils are composed of lymphoid structures closely resembling in their general anatomy Peyer's patches of the small intestine.[1]

The physiological activities of the tonsils have been variously interpreted by different investigators. The older view, now discredited, assumed that they were secreting organs furnishing a thick, viscid mucus. Later, Kingston Fox,[2] Hill,[3] and Spicer[4] advanced the view that these structures reabsorb the waste secretions of the neighboring

[1] For a consideration of the anatomy of the normal pharyngeal tonsil, with bibliography, consult Gottstein and Heymann's Handbuch der Laryngologie und Rhinologie, Wien., 1899, Bd. ii. S. 534.

[2] Fox. Journal of Anatomy and Physiology, London, 1885-86, vol. xx. p. 559.

[3] Hill. British Medical Journal, 1888, vol. iii. p. 615

[4] Spicer. Lancet, 1888, vol. ii. p. 805.

parts. More recently the question of absorption through the tonsils has been the subject of still more important researches. Studies in this direction by Ruffer,[1] Gulland,[2] Goodale,[3] and Hendelsohn[4] show that foreign materials, such as carmine, soot, and cinnabar, may be absorbed from the surface of the faucial tonsil in a short time after their application.

Goodale, in a series of interesting experiments in which he injected carmine particles into the tonsillar crypts, and after a time varying from a few minutes to several weeks, removed the tonsils and examined them microscopically, came to the following conclusions: 1. Absorption takes place normally through the mucous membrane of the lacunæ. 2. It follows the line of direction of the connective tissue. 3. The multinuclear leucocytes take a part in the process. 4. Bacteria are usually found in the lacunæ, but are not easily recognizable in the tonsillar tissue.

This observer's main conclusions have been confirmed by Labbé and Levi-Sirugue;[5] and Hendelsohn[6] has further shown that the pharyngeal tonsil also absorbs foreign particles. While Goodale claims that particles may be absorbed through the normal mucosa of the crypts, Hodenpyl[7] concluded, from experiments made in 1891, that absorption does not occur through the normal mucosa. He believes, however, that substances finding their way beneath the epithelium, chiefly on account of the rarefaction of the epithelium, may be taken up rapidly by the lymphatics. Most recent observers favor the view advanced by Goodale.

There has also been much discussion as to the importance of different cells in the absorption of material from the tonsil surface. Statements as to the presence of foreign material within the leucocytes of the submucous tissues and of the lymph-adenoid tissue of the tonsil are somewhat at variance, some authors stating that they found it within polymorphonuclear cells. The character of the leucocytes within the tonsil in health and disease is one, however, that cannot be said to be definitely settled, although the more recent work with more elaborate methods of staining suggests that the leucocytes within the tonsils are not of the form which ordinarily in other portions of the body are considered to have phagocytic action.

In order to test the significance of the migration of leucocytes, Hendelsohn[8] injected emulsions of soot and cinnabar into the tonsils, and found that so little of the material was taken up by the leucocytes and

[1] Ruffer. British Medical Journal, 1890, vol. ii. p. 491.
[2] Gulland. Edinburgh Medical Journal, 1891, vol. i.
[3] Goodale. Arch. of Laryngologie u. Rhinologie, Bd. vii., Heft 2, p. 90.
[4] Hendelsohn. Arch. of Laryngologie u. Rhinologie, Bd. viii., Heft 3.
[5] Labbé and Levi-Sirugue. Bull. et Mém. Soc. d'Anat., 1889, tome lxxiv. p. 685.
[6] Hendelsohn. Loc. cit.
[7] Hodenpyl. THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, 1891, vol. ci. p. 257.
Hendelsohn. Loc. cit.

carried to the surface that the migration of these bodies was not considered as a protective action.

Altogether, these investigations show that in the reticular tissue of the normal tonsil there are found typical lymphocytes, a few eosinophiles (varying in number with the species of animals examined), with no polymorphonuclear leucocytes. The lymphocytes being in other situations non-phagocytic, this migration of the leucocytes has not been looked upon as being actively protective. The reason for the migration is still to be discovered.

Pathology of Simple Adenoids. *Frequency.* According to Zarnico[1] and others, adenoids occur most frequently between the ages of five and fifteen, less frequently before five and after fifteen. They are said by Frankel[2] to occur at birth and are not very rare after middle age.

An analysis of six hundred cases in the children's section of the Vanderbilt Clinic shows adenoids occurring thirty-five times in all classes of disease (5 per cent.). We believe that this is too low an estimate, for, necessarily, in a general clinic these growths are often overlooked in the presence of an acute and for the moment more important condition.

An analysis of one thousand cases in the throat and nose department of the same institution, reported from June, 1900, to January, 1901, gave eighty-five adenoids, or 8.5 per cent. From the nature of the examination in this class of cases it is highly probable that none was overlooked. The ages of these cases were as follows:

Up to and including five years	36
Five to ten years	19
Ten to fifteen years	24
Over fifteen years	6
	85

Youngest case, nineteen months; oldest, twenty-nine years.

That the condition is not frequent under one year is shown by the result of examination of one hundred cadavers of this age at the New York Foundling Hospital. In these no adenoids were found, although in this institution the condition is frequently met with between the age of three and four years. As to the frequency of adenoids in persons otherwise considered healthy, Meyer found them in 1 per cent. (1000 cases), Schmiegelow in 5 per cent. (581 cases), Wroblenski in 7 per cent. (650 cases), Rosenberg in 15,000 cases, 1350 times (9 per cent.), and Chappel found them present in 3 per cent. out of 2000 New York school-children examined.

[1] Zarnico. Lehrbuch der Krankheiten der Nasen.
[2] Frankel. Zeitsch. f. Ohrenheilkunde, 1881, Bd. x. S. 113.

MORPHOLOGY OF SIMPLE ADENOIDS. Adenoids have already been the subject of several illuminating microscopical studies, and, on the whole, our own studies do no more than confirm previous histological observations.[1]

Adenoid vegetations consist essentially of hyperplastic pharyngeal lymphoid tissue; aside from this they present other more or less constant morphological features.

MATERIAL AND METHODS EMPLOYED. The basis of our remarks upon the histology of simple adenoids is the study of forty-six specimens. The gross features of each adenoid were first carefully noted, and then each was immediately placed in 95 per cent. alcohol, embedded in celloidin, and finally stained with hæmatoxylin and eosin, and picro-acid fuchsin. Ten sections at least from as many different portions of each adenoid were examined.

EPITHELIUM. The epithelial layer is subject to considerable variation from the existence of concomitant processes but chiefly mechanical influences, such as pressure. Both the thickness of the epithelium and the morphology of the cells were different in the various specimens. In the same specimen the degree of thickness may also widely vary; thus in a portion only one or two layers of cells may be present, while elsewhere so many as ten or even more may be seen. Either ciliated, columnar, or flat, squamous epithelium may constitute this layer; or between these two forms many intermediate shapes may be noted.

McBride and Turner[2] state that the thickening occurs especially in children under ten or twelve years of age; on the other hand, in patients upward of fifteen years old they found no lesions of this sort. From these and other observations they conclude that changes of this kind are not necessarily dependent upon the age of the adenoid. Our own experience confirms this view, and further seems to indicate the greater frequency of this epithelial thickening in young children as compared with older ones.

Of the forty-six specimens studied, thirteen presented epithelium about normal for this portion of the pharynx; five of these showed the mucous cells described by Brindel.[3] Thirty-two specimens revealed a greater or less amount of squamous epithelium on the surface; the epithelial recessions (crypts) were involved in none of these specimens. Small and superficial areas of mucous membrane necrosis were occasionally noted, with slight neighboring polymorphonuclear cell infiltration. Bacteria, mainly cocci, were usually present in the necrosed and subjacent tissue. Slight polymorphonuclear and mononuclear cell

[1] Vide Brindel. Revue hebd. de Laryng., d'Otologie et du Rhin., 1896, vol. xvi. p. 881. Also McBride and Turner, Edinburgh Medical Journal, May, 1897, vol. i. p. 355. Baup, Les Amygdales porte d'entree de la Tuberculose. Thèse de Paris, 1900.

[2] McBride and Turner. Op. cit.

[3] Brindel Loc. cit.

infiltration was also observed in a few specimens between the normal epithelial cells. Baup,[1] accepting the conclusions of Labbé and Levi-Sirugue,[2] believes some of these cells to be of epithelial derivation. We have not seen any evidence in our specimens sustaining such an assumption.

Karyokinetic figures were occasionally noted in the deeper layers of epithelium.

Almost all the specimens examined in this study showed a more or less distinct basal membrane beneath the epithelium. In the adult, Moure[3] states that there often exists connective tissue strands separating the lymphoid from the epithelial tissue. This was not observed in the specimens examined by us.

Lymphoid Tissue. Apart from greater or less hyperplasia of the lymphoid cells, few very definite lesions were observed in the series of specimens. The cells were for the most part closely packed, sometimes showing swelling, necrosis, or mitotic figures. Intermingled with the parenchyma cells, polymorphonuclear leucocytes were often noted, almost always in small numbers. In two specimens in which the fibrous tissue reticulum was considerably increased, eosinophile cells were present in moderate numbers, scattered irregularly through the tissues. Several lesions strikingly similar to those first described by Oertel in the lymphatic apparatus of the body in diphtheria were studied in Specimen 1; this adenoid contained the streptococcus pyogenes.

The Relative Amount of the Lymphoid and the Fibrous Tissues. The amount of fibrous tissue present in adenoids is variable; in many cases it is extremely scanty and in others very abundant. The relation of such an increase to the disappearance of adenoids is one of considerable interest. Therefore, we give the results of our observations in this connection of the forty-five specimens studied. Twenty-nine (64 per cent.) showed noteworthy increase of the fibrous tissue, largely perivascular in distribution; in eleven of these the increase was very great and usually associated with some thickening of the bloodvessels.

Brindel[4] found evidence of fibrous tissue increase in forty out of sixty-four specimens examined, and McBride and Turner[5] observed it in at least 50 per cent. of all specimens taken from children under seven years. Cornil and Ranvier[6] and Gottstein[7] have also described this connective tissue increase. These, the observations of Baup[8] and our

[1] Baup. Les Amygdales porte d'entree de la Tuberculose. • Thèse de Paris, 1900, p. 24.
[2] Labbé and Levi-Sirugue. Bull. de la Soc. Anat., July, 1899.
[3] Moure. Bull. de l'Acad. Med., Paris, 1895, p. 570.
[4] Brindel. Loc. cit.
[5] McBride and Turner. Op. cit.
[6] Cornil and Ranvier. Histologie pathologique. Paris.
[7] Gottstein. Berlin. klin. Woch., 1896, Bd. xxxiii. S. 689.
[8] Baup. Op. cit.

own observations for the most part seem to indicate a greater frequency of such change in the young as compared with adults. It is to this process of fibrosis that the shrinking of adenoids has often been attributed.

Thus, H. Norval Pierce[1] states that in early life the connective tissue is embryonal in type, and matures later, when, as usual in new-formed connective tissue, it ultimately contracts, squeezing the lymph nodules and shutting off the blood supply, thus leading to atrophy. Baup considers it a reparative process. In our opinion, this is probably occasionally one of the factors inducing disappearance of the hyperplastic lymphoid tissue, but by no means the only one. Small atrophic adenoids have been studied by us, but in some we were unable to observe any large amount of fibrous tissue.

Blood and Lymph Vessels. Fibrous thickening of the bloodvessels was noted in seventeen of the specimens; in eleven of these concomitant fibrosis of the whole tissue was present. The bloodvessels on the other hand were sometimes slightly involved and without any fibrosis of the tissues elsewhere. Swelling of the blood and lymph vessel endothelium existed in some of the specimens, but in none to a very marked degree except in one which contained lesions similar to those described by Oertel in diphtheria. Evidences of endothelial cell phagocytosis were frequently observed.

Bacterial Infection of Adenoids. In order to determine whether or not bacteria other than the tubercle bacillus might be present within the hyperplastic pharyngeal lymphoid tissue, eleven medium-sized adenoids, not included in the previous series, were submitted to bacteriological examination. They were all removed from children apparently otherwise well.

Technique. The adenoids immediately after removal were placed in sterile bottles and bacteriological examinations were begun in all instances within two hours after their removal. The surface of the tissue was seared with a hot knife and portions of tissue were then removed from the interior of the adenoid with a sterile platinum loop needle; liberal quantities were removed in each instance. The removed material was then carefully broken up into fragments in tubes of sterile broth, and from the latter aërobic agar plates of varying dilutions and tube blood-serum cultures were made. The adenoids, immediately after having removed the tissue for culture purposes, were placed in 95 per cent. alcohol. Series of sections (ten to thirty) from each adenoid were stained by Weigert's modification of Gram's method and with Loeffler's methylene blue. The classification of each identified micro-organism was based on a complete study of the morphological, tinctorial, and

[1] Pierce. Journal of Laryngology, January, 1901.

cultural features presented by the bacterium. Animal experiments were further made in some instances to determine the virulence of the organism studied. Cover-slip controls from the fresh tissue were made in each instance.

RESULTS. The tube and plate cultures from five of the eleven specimens remained sterile after ten days' incubation at 37° C. The remaining six specimens gave the following results:

No. of specimen.	Amount of growth.	Predominating organism.	Bacteria found.
1	Two colonies.	Streptococcus pyogenes.	Streptococcus pyogenes.
2	Very scanty.	Streptococcus pyogenes.	Streptococcus pyogenes and staphylococcus pyogenes aureus.
6	Abundant.	Unidentified bacillus, short, thick, not decolorized by Gram.	Unidentified bacillus; diplococcus lanceolatus, and staphylococcus pyogenes aureus.
7	Scanty.	Diplococcus lanceolatus.	Diplococcus lanceolatus and staphylococcus pyogenes aureus and albus.
10	Moderate.	Streptococcus pyogenes.	Streptococcus pyogenes.
11	Scanty.	Staphylococcus pyogenes albus.	Staphylococcus pyogenes albus.

The streptococcus pyogenes cultivated from Specimen 1 did not kill a rabbit (1210 grammes) which had been inoculated intravenously with 2 c.c. of a forty-eight-hours' bouillon culture. Another streptococcus from Specimen 10 similarly inoculated in the same dose into another rabbit (992 grammes) induced no apparent reaction. The diplococcus lanceolatus from Specimen 7 failed to kill a rabbit (1355 grammes) inoculated under the same conditions.

EXAMINATION OF THE SECTIONS FOR BACTERIA. The recognition of bacterial forms was often extremely difficult and uncertain. With the exception of Specimens 1 and 6 of the above table, the bacteria were few in number and seemed to be mainly limited on the outside of or just beneath the surface epithelium. For the most part, coccal forms only were observed. They were noted in greater abundance in the crypts along with epithelial cells, leucocytes, and débris. Now and then micro-organisms were made out between the epithelial cells, especially in the crypts and where the epithelium was thinner than normal. Specimens 1 and 6 contained several foci of bacteria, mainly cocci without any distinct evidence of inflammatory reaction around them. A few polymorphonuclear leucocytes were observed in the vicinity. In both specimens the bacterial masses were near the surface. Sections from two of the specimens revealed a few bacteria (cocci and short, thick bacilli) on the surface, and here and there between the cells of the epithelial layer.

Goure,[1] whose studies included a large number of specimens, found micro-organisms in a still greater percentage of the adenoid growths investigated. Two hundred and one specimens were studied by coverslips and cultures on blood-serum. His results were as follows:

Twenty-five cultures contained no growths.

Streptococci (never alone) with other bacteria, 37 times.

Staphylococci alone, 69 times.

Staphylococci with other bacteria, 69 times.

Various other cocci (diplococci, tetrads) alone, 41 times.

Various other cocci (diplococci, tetrads) with other bacteria, 54 times.

Pneumococcus alone, 3 times.

Leptothrix buccalis alone, 2 times.

Leptothrix buccalis with other bacteria, 1 time.

PRIMARY TUBERCULOSIS OF THE PHARYNGEAL LYMPHOID TISSUE. In the following résumé only the literature of primary tuberculosis of the pharyngeal tonsil is considered. For a discussion of this lesion in the faucial tonsil, consult the admirable article by Friedmann,[2] which contains the results of original study, and a very complete bibliography.

PREVIOUS STUDIES. Although William Meyer[3] and Trautman[4] were both of the opinion that adenoids were in some way related to so-called scrofula, the latter after careful search was unable to find any evidence of tuberculosis in the hyperplastic pharyngeal lymphoid tissue of such cases. Passing over the work of the numerous observers who found evidence of tuberculosis in this tissue in tuberculous subjects, we find several writers—Wendt,[5] Megevand,[6] Suchannek,[7] Dmoschowski[8]—describing isolated cases of primary tuberculous infection of adenoids. These, according to Piffl,[9] are the first reported observations on this subject.

In 1892 Pilliet[10] studied, by histological methods, ten specimens of adenoids removed from as many persons, and found one containing giant cells and necrosis. The next investigation, also wholly histological in character, was made by Lermoyez,[11] who examined thirty-two

[1] Goure. L'Amygdale de Meyer; Annales de maladies de l'oreille et du larynx, 1897, tome xxiii. p. 437.

[2] Friedmann. Beitrage zur Path. Anat. u. z. allg. Path., 1900, Bd. xxviii. S. 66; also Labbé and Levi-Sirugue, Gaz. des Hôp., 1900, No. 20, p. 193.

[3] Meyer. Op. cit.

[4] Trautman. Anat. path. u. klin. Studies über Hyperplasis de Rachentonsil, Berlin, 1896. Handbuch d. Ohren. v. Schevartze, 1893, Bd. ii. S. 135.

[5] Wendt. Ziemssen's Handbuch, 1874, Bd. vii.

[6] Megevand. Contribution a l'Étude des maladies de la voute et du pharynx, Geneva, 1887.

[7] Suchannek. Ziegler's Beitrage, 1888, Bd. iii.

[8] Dmoschowski. Ibid., 1891. Bd. x.

[9] Piffl. Zeitsch. für Heilkunde, 1899, Bd. xx. S. 297.

[10] Pilliet. Bull. de la Soc. Anat., Paris, 1892, tome vi. p. 236.

[11] Lermoyez. Bull. et mém. Soc. méd., Paris, 1894, tome xi. p. 559.

specimens, two of which showed morphological evidence of tuberculosis. The studies of Dieulafoy[1] quickly followed and were based entirely on the results of animal inoculations. Seven (20 per cent.) of the specimens showed tuberculous lesions.

It was not until later that a real and wide-spread interest was taken in the matter.

Quickly following these reports came that of Pilliet's,[2] who had examined by sections another series of forty specimens. In none did he find any evidence of tuberculosis. Brieger[3] examined seventy-eight specimens and found morphological evidence of tuberculosis in five. Moure,[4] on the other hand, by a study of sections from forty specimens, succeeded in finding tuberculous lesions in only one. By similar study of one hundred specimens, Broca[5] did not find evidence of tuberculosis in a single one. But Gottstein,[6] with his series of thirty-three specimens, was much more fortunate. The examinations were entirely histological, but he found three specimens containing lesions morphologically characteristic of tuberculosis.

Pluder and Fischer,[7] from the histological examination of thirty-two adenoids, found five to be tuberculous, 16 per cent. Tubercles were found only in the lymphoid tissue of the mucosa and never in the deeper portions. Bacilli were present only in the affected parts and in small numbers; they were never found in the epithelium or healthy lymph follicles. The nasal and pharyngeal mucus did not show bacilli. The writers regard these cases as true examples of primary tuberculosis, as all the patients were otherwise healthy.

Brindel,[8] with his sixty-four cases, found 12 per cent. tuberculous. The diagnosis was based on finding giant cells, etc. Bacteriological examinations were made in but one case; inoculations in none. Luzzatti[9] investigated by section study fifty adenoids, but failed to find any showing tuberculous lesions.

Gourc[10] examined two hundred and one cases; eighteen of the individuals had hereditary (?) and seventeen acquired tuberculosis. He made use of cultures, inoculations, and histological examinations without finding evidence of tuberculosis. In none did he find any evidence of tuberculosis. He concludes that while he cannot deny the occurrence of tuberculous infection of adenoids it is extremely rare.

[1] Dieulafoy. Bull. de l'Acad. Méd., Paris, 1895, tome xxxiii. p. 437.
[2] Pilliet. Discussion by Cornil. Bull. de l'Acad. Méd., Paris, 1895, p. 498.
[3] Brieger. Verhandl. deutsch. Otol. Gesellsch., Jena, 1895, also 1898.
[4] Moure. Bull. de l'Acad. Méd., Paris, 1895, p. 570.
[5] Broca. Annales de mal. de l'oreille et du larynx, 1896, tome xxii. p. 317.
[6] Gottstein. Berlin. klin. Woch., Bd. xxxiii. S. 689.
[7] Pluder and Fischer. Arch. of Laryng. u. Rhinologie, 1896, Bd. iv. S. 372.
[8] Brindel. Revue hebd. de Laryng., d'Otologie et du Rhinologie, 1896, tome xvi. p. 881.
[9] Luzzatti. Giornale dell Academie Med. di Torino, 1897, Nos. 7-9.
[10] Gourc. Thèse de Paris, 1897.

McBride and Turner[1] examined one hundred adenoids and found three with lesions of tuberculosis. The diagnosis of the lesion was based entirely on morphological considerations. No tubercle bacilli were found in any of the sections.

In a series of two hundred specimens investigated by Lewin,[2] evidence of tuberculosis was found in ten; twenty of the specimens were studied by animal inoculations, with one positive result; the remainder were examined only histologically. This observer reached the following conclusions:

1. Five per cent. of the hyperplastic pharyngeal tonsils contain tuberculous lesions.

2. The lesion resembles the so-called tumor form of tuberculosis of mucous membranes. It is characterized by the absence of all recognizable external signs—"latent" tuberculosis of the tonsils.

3. This latent tuberculosis may apparently be the first and only lesion of tuberculosis in the body.

4. It is usually associated with more extensive tuberculosis of other organs, especially of the lungs, although this at the time of operation is often not apparent.

5. Tuberculosis of the pharyngeal tonsil is relatively frequent in pulmonary tuberculosis.

6. The tuberculous process may affect normal tonsils as well as hyperplastic ones. It is doubtful whether the toxins induce the hyperplasia. The tuberculous process may delay the involution of the hyperplastic tonsil.

7. The tubercle bacillus plays very little part in the etiology of pharyngeal tonsil hyperplasia.

8. The tuberculous lesion may be entirely removed by extirpation of the tonsil.

Scheibner[3] also, by histological methods, examined fourteen adenoids, in none of which he found any lesion of tuberculosis.

Piffl[4] examined one hundred adenoids taken from clinics and private practice. Three showed histological tuberculosis, 3 per cent. No animal inoculations were made. Seven of the patients had tuberculosis. All the sections were stained for bacilli. The epithelium showed many defects and contained "becherzellen" of different sizes. One tuberculous adenoid showed tubercle bacilli, and all three specimens caseation and miliary tubercles.

Wex,[5] in a series of examinations of stained sections from two hun-

[1] McBride and Turner. Op. cit.
[2] Lewin. Arch. of Laryng. u. Rhinologie, 1899, Bd. ix. S. 377.
[3] Scheibner. Deutsch. med. Woch., 1899, Bd. xxv. S. 343.
[4] Piffl. Zeitsch. f. Heilkunde, Bd. xx. S. 297.
[5] Wex. Zeitsch. für Ohrenheilk., 1889, Bd. xxxiv. S. 207.

dred and ten cases, found seven specimens tuberculous, 3.33 per cent. In six of these bacilli were found. He found also a number of other adenoids that showed giant cells only, and which he does not consider proper to class as tuberculous. Hynitsch[1] similarly examined one hundred and eighty pharyngeal tonsils; seven were found to be tuberculous, 3.9 per cent. Tubercle bacilli were found in only three of the specimens.

Baup[2] made sections from forty-eight adenoids, forty-five of which he also inoculated into guinea-pigs. Only one positive result was obtained.

J. Wright[3] studied fifty-one adenoids, most of them by section study only, a few by animal inoculations, but in none was he able to demonstrate any evidence of tuberculosis.

Another study of eighty-five adenoids by Dr. George Blumer,[4] of the Bender Hygiene Laboratory, Albany, New York, revealed four containing tuberculous lesions; histological studies alone were made, and in each case tubercle bacilli were demonstrated in the sections. This gives 4.7 per cent. of tuberculous adenoids.

Writers' Studies. Seventy-five consecutive specimens of adenoids were tested for tuberculosis. About two-thirds of them were obtained from the Children's and from the Nose and Throat Departments of the Vanderbilt Clinic, New York City, and the remainder from the New York Foundling Hospital, the New York Eye and Ear Infirmary, and from several private sources.[5] So far as could be ascertained the children from whom the specimens came were, aside from the adenoid trouble, quite healthy.

Methods of Procedure. The material was collected immediately after operation in clean bottles. As soon as possible thereafter the whole adenoid was carefully washed by repeated shakings in sterile normal salt or Dunham's solution. It was then placed in a sterile Petri dish, cut into four equal parts with sterile instruments, using the alternate pieces for inoculation purposes; the remainder was placed in 95 per cent. alcohol for subsequent histological examination. With the exception of the first seven specimens the portion of tissue set aside to be inoculated was reduced to a pulp, the juice therefrom filtered through sterile cheese-cloth, and the filtrate was then inoculated beneath the skin of the groin of a guinea-pig. In the first seven cases the alternate pieces were merely introduced subcutaneously without

[1] Hynitsch. Zeitsch. für Ohrenheilk., 1899, Bd. xxxiv. S. 184.
[2] Baup. Op. cit.
[3] Wright. New York Medical Journal, 1900, vol. lxxi. p. 508.
[4] Blumer. Personal communication.
[5] For most of the material investigated we are greatly indebted to Drs. Huber and Simpson, of the Vanderbilt Clinic, and also to Dr. Holt, of the New York Foundling Hospital, and Dr. Mayer, of the New York Eye and Ear Infirmary.

reducing to a pulp. All the animals were kept under the same conditions.

Two animals died on the sixteenth and twentieth days, respectively; but in both instances careful microscopical and histological study of the tissues, including seats of inoculation, failed to show any tuberculous lesion or tubercle bacilli. All the other animals died or were killed after the twenty-seventh day; most of them, however, died or were killed after the fortieth day. The presence or absence of tuberculosis in the inoculated animals was always tested by microscopical examination of the tissues at the seat of inoculation and elsewhere. Tubercle bacilli were always demonstrated in the lesions of the positive cases.

Pieces of hardened adenoid tissues were embedded in celloidin and stained with hæmatoxylin and eosin for general morphology; and Ziehl-Neelsen's method was employed for the demonstration of tubercle bacilli in the tissues. Tubercle bacilli were looked for in the section of only those specimens which induced tuberculosis in the guinea-pigs, since it was assumed that the far more delicate inoculation test was decisive. Sections from those specimens were persistently stained until tubercle bacilli could be demonstrated. Upward of one hundred and twenty-five sections were thus examined in cases 35 and 55, respectively, before this organism was found in the tissues, and then only in small numbers.

Results of the Animal Experiments. Out of the seventy-five specimens tested, twelve induced tuberculosis in the inoculated animals; hardened tissues of eight of the specimens contained both tubercle bacilli and lesions histologically more or less characteristic of tuberculosis.

The remaining four specimens contained tubercle bacilli, but presented no histological evidence of tuberculous lesions.

Morphology of the Tuberculous Adenoids. Of the twelve specimens which contained tubercle bacilli, only eight showed histological lesions of tuberculosis—giant cells, caseation, and epithelioid cells. In the remaining four specimens none of these elements were observed in those portions containing tubercle bacilli or elsewhere. In all cases the bacilli were more or less close to the surface and few in number; the lesions of seven cases were likewise peripherally situated, close to the epithelium and quite focal in character. Four showed single tubercles; in two of the specimens the histological lesion was diffuse but not extensive. One specimen only showed a lesion in the middle of the adenoid tissue, consisting of a single tubercle.

The morphology of the tubercles was generally characteristic; almost all seemed to be of recent formation. Very little caseation was noted; and giant cells were few in number or not present.

TABLE OF RESULTS.

	Specimen.	Source.	Time animal was observed.	Autopsy finding.	Histological tubercle.
1	4	Foundling Asylum.	Killed 32d day.	Generalized tuberculosis.	Several.
2	9	Foundling Asylum.	Died 27th day.	Generalized tuberculosis.	Several.
3	23	Vanderbilt Clinic.	Died 33d day.	Tuberculosis at seat of inoculation and abdominal glands.	One.
4	27	Dr. M.	Died 24th day.	Tuberculosis at seat of inoculation.	None.
5	36	Vanderbilt Clinic.	Killed 49th day.	Generalized tuberculosis.	None.
6	38	Foundling Asylum.	Died 20th day.	Tuberculosis at seat of inoculation, and abdominal lymph nodes.	Several.
7	42	Foundling Asylum.	Died 30th day.	Tuberculosis at seat of inoculation, spleen, lymph nodes.	One.
8	49	Foundling Asylum.	Died 38th day.	Generalized tuberculosis.	None.
9	51	Dr. B.	Killed 27th day.	Tuberculosis at seat of inoculation, and lymph nodes.	One.
10	55	Vanderbilt Clinic.	Died 16th day.	Tuberculosis at seat of inoculation.	None.
11	63	Vanderbilt Clinic.	Died 25th day.	Tuberculosis at seat of inoculation, and lymph nodes.	Several.
12	71	Vanderbilt Clinic.	Died 29th day.	Generalized tuberculosis.	One.

Unless the lymphoid hyperplasia, at all events a part of it, be considered in the four specimens presenting no typical tuberculous lesion as having been induced by the bacillus tuberculosis—and such tissue changes following tubercle bacillus infection are by no means uncommon, especially in lymph nodes—then in these cases no lesion can truly be said to have developed. Nearly all observers agree as to focal character of the lesions.

The following gives the percentage results:

Total number of specimens tested	75	
Number containing bacilli and showing histological lesions of tuberculosis	8 = 10.67	per ct.
Number containing bacilli but no histological lesions	4 = 5.33	"
	12 = 16.00	"

THE VIRULENCE OF THE TUBERCLE BACILLI. The tubercle bacilli present in Specimens 4, 38, and 63 were especially studied with a view to determine their virulence.

METHODS OF PROCEDURE.[1] Cultures were usually obtained from the deep inguinal or sublumbar lymph nodes of guinea-pigs previously

[1] Vide Lartigau. A Study of the Variations in Virulence of the Bacillus Tuberculosis in Man. Journal of Medical Research, 1901, vol. vi. No. 2.

inoculated with tuberculous material. Cultivation was made on 6 per cent. glycerin agar-agar. From fifteen to thirty tubes were always inoculated, for very often, especially with the more virulent bacilli, development took place in one or two of the tubes only. In all cases the growth was continued until it became voluminous (four to eight weeks).

For purposes of comparative study by inoculation with the guinea-pig and rabbit, the solid masses of culture were scraped off from the moist agar, especial care being taken only to remove bits of culture free from any of the medium. Usually 5 milligrammes of the tubercle bacillus were then carefully weighed and finely suspended in 5 cubic centimetres of an indifferent fluid, such as physiological salt solution, until the density was quite uniform and microscopical examination showed no (or very few) clumps. The mixture was quickly used when prepared. Occasionally, when large amounts of the tubercle bacillus were to be inoculated, 10 or more milligrammes were weighed out instead and suspended in the same amount of fluid. If, on the other hand, small amounts of the bacillus were to be utilized, then the 5 milligrammes were suspended in 10 cubic centimetres of the salt solution. Thus, in the latter case, 10 cubic centimetres of the emulsion would equal 5 milligrammes; 5 cubic centimetres would equal 2.5 milligrammes; 1 cubic centimetre would equal 0.5 milligramme; ½ cubic centimetre would equal 0.25 milligramme, etc. Dosage under these conditions was then always fairly accurate.

The comparative method of inoculation recommended by Arloing[1] was in other respects rigorously adhered to when this was in view; the guinea-pigs and rabbits were inoculated in pairs in the same region, with the same quantity of culture and at the same time; all inoculated animals were kept under essentially the same conditions.

The presence or absence of tuberculosis in the inoculated animals was always based on both naked-eye appearances and microscopical examinations; identification of the tuberculous lesion was always confirmed by finding tubercle bacilli in the affected tissues. Cultures were obtained from the tuberculous lesions of the livers or spleens of the guinea-pigs, except when the tuberculosis was confined to the seat of inoculation; when the latter was the case, the cultivation, perforce, was made from this focus. To recapitulate, the method of procedure in the animal tests was as follows: The inoculations were made in series, one guinea-pig and one rabbit usually constituting the animals for each set. A definite and small amount of culture was inoculated into each animal under the same experimental conditions. From the guinea-pig of the first set cultures were again obtained and a second set of animals

[1] Arloing. Leçons sur la Tuberculose et certaines Sépticémies, Paris, 1892, p. 161.

reinoculated under the same conditions; from the guinea-pig of the second set cultures were prepared and inoculated into a third set. This was not carried beyond the third set. The channel of infection was subcutaneous.

EXPERIMENTAL RESULTS. The results of the animal inoculations showed that the tubercle bacillus from Specimen 4 was moderately virulent. Doses of 10 milligrammes introduced beneath the skin induced only slight general tuberculosis. The bacilli from Specimens 38 and 63, on the other hand, were both of low virulence; doses of 10 or 20 milligrammes inoculated subcutaneously induced little tuberculous inflammation, usually limited to the seat of inoculation.

	Series.	Animal.	Inoculated, dose.	Died.	Autopsy findings.
Tubercle bacillus from specimen 4	1	Rabbit, 1105 grams.	20 mg.	41st day	Moderate tuberculosis of lungs and spleen and inoculation seat.
		Guinea-pig, 455 grams.	20 mg.	23d day	Moderate generalized tuberculosis.
	2	Rabbit, 1080 grams.	10 mg.	48th day	Tuberculosis of lungs and inoculation seat.
		Guinea-pig, 485 grams.	10 mg.	18th day	Tuberculosis inoculation seat, and abdominal lymph nodes.
	3	Rabbit, 1210 grams.	10 mg.	53d day	Slight tuberculosis of lungs, kidney, spleen, and inoculation seat.
		Guinea-pig, 575 grams.	10 mg.	30th day	Tuberculosis of inoculation seat, abdominal lymph nodes, lungs, and spleen.
Tubercle bacillus from specimen 38	1	Rabbit, 1340 grams.	20 mg.	38th day of other disease.	Tuberculosis inoculation seat and one nodule right lung.
		Guinea-pig, 620 grams.	20 mg.	24th day	Tuberculosis inoculation seat, abdominal lymph nodes, and liver.
	2	Rabbit, 1160 grams.	19 mg.	62d day killed.	Tuberculosis inoculation seat.
		Guinea-pig, 530 grams.	10 mg.	33d day	Moderate tuberculosis inoculation seat, and abdominal lymph nodes, and liver.
	3	Rabbit, 940 grams.	30 mg.	56th day	Moderate tuberculosis inoculation seat, spleen, liver, and lungs.
		Guinea-pig, 575 grams.	30 mg.	26th day	Moderate tuberculosis inoculation seat, liver, lungs, and abdom'l lymph nodes.
Tubercle bacillus from specimen 63	1	Rabbit, 1280 grams.	20 mg.	48th day	Tuberculosis inoculation seat.
		Guinea-pig, 735 grams.	20 mg.	39th day	Tuberculosis inoculation seat and abdominal lymph nodes.
	2	Rabbit, 990 grams.	10 mg.	81st day	Tuberculosis inoculation seat.
		Guinea-pig, 610 grams.	10 mg.	53d day	Tuberculosis inoculation seat, abdominal lymph nodes, and one lung.
	3	Rabbit, 1275 grams.	30 mg.	55th day	Slight tuberculosis inoculation seat and lungs.
		Guinea-pig, 485 grams.	30 mg.	24th day	Generalized tuberculosis.

REMARKS ON PRIMARY TUBERCULOSIS OF THE PHARYNGEAL TONSIL. From the review of previous studies upon tuberculosis of the pharyngeal tonsil, one is much impressed with the lack of thoroughness of many of the investigations and incompleteness of others. The tuber-

culous lesions are usually so focal and discrete, and the tubercle bacilli so few in number in the tissue, that most searching study is necessary to reveal them. This is especially true for lymphoid tissue tuberculosis. The only method, then, which may permit of accurate conclusions is the use of animal inoculations controlled by careful study of many sections of the tissue. Unfortunately, investigations of this kind are too few in number to allow at the present time definite conclusions as to the frequency with which primary tuberculosis of the pharyngeal tonsil occurs. It is especially desirable that in the future the method of investigation be along these lines and uniform, if accuracy is to be attained. It is probable from our experience that many later investigations will show primary tuberculosis in 10 per cent. or over of the clinic cases. Several other factors of importance are to be considered: the evidence of tuberculosis elsewhere in the body and the age of the individuals. The source of the material should also always be mentioned. Obviously, individuals from the poorer classes would show a higher percentage than those living under more hygienic conditions.

Sources of the Bacillus Tuberculosis in Tonsil Infection. As pointed out by Dmoschowski, the sources of infection may be the inspired air, sputum, blood, and lymph.

Inspired Air. The hyperplastic pharyngeal lymphoid tissue lying directly in the path of the inspired air is naturally exposed to infection from this source. That this may be an important source of infection has been shown by Straus,[1] who, in 1894, inoculated a series of animals with the nasal secretion from twenty-nine individuals (themselves not tuberculous) frequenting places where tuberculous patients were living. The enormous number of 40.9 per cent. of all persons experimented upon contained tubercle bacilli in their nasal cavities. Recently, Noble W. Jones[2] has performed similar experiments, using, however, nasal secretions from healthy persons, who, to the best of his knowledge, had not been in contact with tuberculous individuals. Animal inoculations with the secretion from thirty-one persons were made, three animals becoming tuberculous, a percentage of 9.7. The objection that has been brought against this mode of testing in the case of adenoids, viz., that the patients are mouth-breathers, would seem at first glance to be well taken. Pluder and Fischer,[3] however, have shown that mouth-breathing, especially in lower grades of hyperplasia, is not constant. Charles A. Parker found in 82 per cent. of sleeping children that the respiration was nasal, and in 16 per cent. at least partly so. The former writers have also shown that in cases of adenoids the soft palate does not act as a perfect barrier against infection coming through the

[1] Straus. Bull. de l'Acad. de Méd., Paris, 1894, tome xxxii. p. 18.
[2] Jones. Medical Record, 1900, vol. lviii. p. 285.
[3] Pluder and Fischer. Loc. cit.

mouth. They also point to the fact that in many cases of adenoids the nasal passage is widened, thereby increasing the possibility of infection from this source.

The histological study of tuberculous faucial tonsils removed from individuals free from tuberculosis of the lungs also indicates that the process generally extends inward from an infection on the surface.

Sputum. This mode of infection presupposes a primary focus of tuberculosis in the lower respiratory tract or lungs. Secondary infection under these conditions has been frequently demonstrated in cases of pulmonary tuberculosis with free expectoration, notably by Strassmann, Dmoschowski, Schlenker, Kruckmann, Suchannek, Wendt, Megevand, Piffl, Habermann, and Fraenkel.

Lymph and Blood. Infection through the lymph and blood would naturally be most likely to occur in connection with acute general miliary tuberculosis. Habermann and others believe that infection can take place from the middle ear, presumably through blood or lymph channels.

Dmoschowski[1] has demonstrated bacilli in the lymph channels connecting the tonsils with the cervical glands, and Piffl[2] has described an ascending tuberculous infection of the lymph passages from the mediastinum. Scheibner[3] and others have observed tuberculous infection of the tonsil in cases of miliary tuberculosis of short duration, in which, of course, infection from the sputum must be excluded, but which the writers believe to have been true cases of blood and lymph infection. Until more accurate observations have been made, especially with regard to the relative ages of coexisting lesions, the frequency of this mode of infection cannot accurately be determined. In general, it may be said that the majority of observers are agreed that in the case of tuberculous individuals with free expectoration the infection of the pharyngeal tonsil in all probability practically always comes from the latter source, while in individuals without lung tuberculosis the factors previously mentioned, together with certain histo-pathological findings, go to show that the source of infection is almost always from the inspired air.

THE TONSILS AS SEATS OF INFECTIONS AND PORTALS OF ENTRY OF MICRO-ORGANISMS. *Miscellaneous Bacteria.* The nasopharyngeal cavity presents several anatomical and physiological peculiarities which predispose to primary infection: 1. The presence of lymphoid tissue whose surface is not smooth, but which is provided with crypts and irregular depressions. 2. The surface is not lined with ciliated epithelium throughout. In the crypts, especially in the young, flat epithelium

[1] Dmoschowski. Beitrage z. path. Anat. u. z. allg. Path., Jena, 1891, Bd. x. S. 481.
[2] Piffl. Loc. cit.
[3] Scheibner. Deutsch. med. Woch., 1899, Bd. XXV. S. 343.

may occur; and (3) catarrhal conditions often arise in the nasopharyngeal mucous membrane, leading to epithelial denudation. The great liability of the tonsils to mechanical lesions necessarily also increases the predisposition to infection. These considerations apply to the pharyngeal tonsil as well as to the faucial, and especially to the former when it is in a condition of hyperplasia. The epithelium of the crypts (faucial) and so-called Stohr's canals (pharyngeal) is frequently in young persons changed to the pavement variety instead of the normal ciliated, as McBride and Turner and others have shown. These writers ascribe this change to the friction of opposing surfaces of the tonsils in a condition of hyperplasia and to the pressure of surrounding walls.

Dmoschowski believes that the ciliæ in this region tend rather to work toward the pharynx than outward. Although Hodenpyl's investigations led him to believe that the normal tonsil cannot readily be infected, it has been shown that the tonsils frequently afford places for the lodgement of bacteria because of their irregularity of contour, the presence of lacunar spaces, the rarefaction of the epithelium lining the crypts (Hodenpyl), and the exfoliation of the epithelium which leaves places of denudation. The crypts and canals are deepened and multiplied in the state of hyperplasia, which ensures a better resting-place for infected secretions and dust coming through the nose and mouth. The tonsils are, therefore, constantly exposed to pathogenic organisms contained in the nasal and buccal cavities, and to those in the inspired air and ingested food.

Important protection may be afforded by the wandering leucocytes passing to the tonsil surface, as suggested by the observations of Hugenschmidt.[1] From his experiments he concluded that the saliva possesses positive chemiotatic properties, which explain the diapedesis taking place in the normal tonsil to destroy bacteria. But more important light has been thrown upon this side of the question by the extremely interesting experiments of Manfredi.[2] In a most elaborate article, this investigator argues from the results of his studies that the function of lymphoid tissue is one of protection. He brings forward sufficient evidence to make it probable that such protection occurs in three ways: First, by filtration of the bacteria; second, by an attenuation of the virulence of micro-organisms that reach them; and third, by the whole body obtaining a greater or less immunity while the first two processes are in operation.

As to the capacity for absorption of micro-organisms by the faucial tonsil, Ribbert[3] found that the bacillus of diphtheria is not absorbed in rabbits by the buccal mucous membrane, but may be by tonsils

[1] Hugenschmidt. Annales de l'Inst. Pasteur, 1896, tome x. p. 545.
[2] Manfredi and Viola. Palermo, 1898.
[3] Ribbert. Deutsch. med. Woch., 1897, Bd. xxiii.

whose epithelium shows more or less desquamation. Buschke[1] also concludes that the tonsils are portals of entry for pus-producing organisms. Pluder[2] contends that tonsillar protection to the invasion of bacteria is in reality small, since the tonsils are frequently diseased, and hence portals for the entrance of micro-organisms.

These observations indicate that the faucial and pharyngeal tonsils in the more or less marked pathological condition in which they are often found are frequently open to the invasion of bacteria.

The recent observations of Plottier[3] are of the greatest etiological interest. A series of 268 cadavers of children was examined in respect to adenoid vegetations, and they were only found seven times in fifty-four cases of measles; once in twenty-five cases of gastro-enteritis, in five of scarlet fever, and in twelve of tuberculous meningitis; not at all in five cases of hereditary syphilis and sixteen of athrepsia. On the other hand, they were found six times in twenty-seven cases of bronchopneumonia; five times in twenty cases of pulmonary tuberculosis; three times in seven cases of whooping-cough; and twenty-nine times in fifty-three cases of diphtheria.

Bacillus Tuberculosis. Nearly all observers are agreed that hyperplasia of the pharyngeal lymphoid tissue is very commonly associated with enlargement of the lymph nodes, especially the submaxillary and cervical lymph nodes. Meyer[4] himself vaguely expressed the consideration that tonsillar lymphoid hyperplasia might possibly stand in some relation to scrofula. When the investigations of Baumgarten,[5] Sims Woodhead,[6] and Kruckmann,[7] showing conclusively that micro-organisms may pass through the epithelium of the throat into the cervical lymphatics, are considered in connection with the fact that tubercle bacilli have been demonstrated in a certain number of adenoids, the recent observations of Moore become of great interest. Moore[8] examined superficial lymph nodes removed from twenty cases (eighteen cervical, two axillary). Twenty of these cases were tuberculous; and six of them presented inflammatory lesions of the faucial or pharyngeal tonsil. In one case adenitis appeared to follow adenoids. He believes that in most cases the infection comes from the nose, throat, and mouth, and does not ascend from the mediastinum, the pharyngeal, lingual and faucial tonsils being the chief portals of entry in cervical lymph-node tuberculosis.

[1] Buschke. Deutsch. Zeitsch. für Chir., 1894, Bd. xxxviii.
[2] Pluder. Loc. cit.
[3] Plottier. Revue Hebd. de Laryngologie (Bordeaux), October 14, 1900.
[4] Meyer. Loc. cit.
[5] Baumgarten. Vide Moore.
[6] Sims Woodhead. Report of Royal Commission on Tuberculosis, vol. iii. p. 115.
[7] Kruckmann. Virch. Arch., 1894, Bd. cxxxviii., S. 184.
[8] Moore. Journal of Pathology and Bacteriology, 1900, vol, vi. p. 94.

Jesser[1] believes, as does Zarniko,[2] that in many cases scrofula is the result of an infection from the tonsils, more especially the pharyngeal tonsil. Jesser quotes four very interesting cases in which, after the removal of adenoids in young children, the symptoms of scrofula subsided. The etiological relation of tonsil infection to scrofula is also maintained by Morgan[3] and Gallois.[4]

Delepine and Yonge,[5] on the other hand, examined the tonsils in seventeen cases of tuberculous lymphadenitis without pulmonary tuberculosis, and in none did they find tuberculosis of the tonsils. Like Cheyne,[6] they tend to minimize the importance of tonsil infection in scrofula.

Baup, by introducing tubercle bacilli into the pharynx of dogs, always induced tuberculosis of the cervical lymph nodes; he, therefore, also believes that the tonsils are frequent portals of infection in cervical lymph-node tuberculosis.

Certain writers have also been disposed to lay stress on the tonsils as portals of infection in middle-ear tuberculosis, or Pott's disease (Busse), or meningitis (Demme, Heller, and Ziem).

Conclusions. 1. Adenoids consist essentially of hyperplastic pharyngeal lymphoid tissue. The epithelium and fibrous tissue changes are inconstant and variable, and independent of the age of the patient. The new-formed fibrous tissue is largely perivascular in distribution. It may occasionally be one of the factors in the process of disappearance of the adenoid.

2. The hyperplastic pharyngeal tonsil often contains micro-organisms, and these are mainly pyococcal forms. The bacteria for the most part lie near the surface; and the infection usually occurs from the surface, with or without demonstrable lesion of the epithelium.

3. Primary tuberculosis of adenoids is probably more common than most previous studies show. Sixteen per cent. of our series contained tubercle bacilli, 10 per cent. with characteristic lesions of tuberculosis. The tubercle bacilli were present in small numbers.

4. The lesions in primary tuberculosis of the adenoid are generally close to the epithelial surface and focal in character. Occasionally they may be found in the deeper parts of the pharyngeal lymphoid tissue.

5. The pharyngeal tonsil may be a portal of entry for the tubercle bacillus and other micro-organisms in localized or general infections.

[1] Jesser. Münch. med. Woch., 1898, Bd. xlv. No. 23.
[2] Zarniko. Loc. cit.
[3] Morgan. British Medical Journal, 1899, vol. ii. p. 458.
[4] Gallois. Bull. Med., 1897, p. 1161.
[5] Delepine and Yonge. Vide Moore, Journal of Pathology.
[6] Cheyne. British Medical Journal, 1899, vol. ii. p. 1659.

A CASE OF INTRATRACHEAL COLLOID STRUMA; OPERATION; RECOVERY.*

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Among the problems that the throat specialist is called upon to solve there are few, perhaps, that present more difficulties than some of the conditions causing tracheal stenosis.

A large majority of these cases of tracheal stenosis are due to pressure on the trachea by tumors external to it, to old syphilitic adhesions or gummata, and to certain intratracheal new-growths, benign and malignant.

One of the rarest forms of intratracheal growth, usually causing great stenosis, and making operative procedures imperative on account of the alarming dyspnœa by which it is accompanied, is, without question, the tumor springing from the thyroid tissue in the lower laryngeal cavity and the upper part of the trachea, sometimes called an intralaryngeal or tracheal "accessory" thyroid tumor.

There are now on record, including the case which I have the pleasure of reporting to you this evening, ten positive and two doubtful cases of intralaryngeal and tracheal tumors, originating in thyroid tissue. Eight of these were observed in different parts of Germany.

The author's case is the second reported in the United States, and the tenth on record. The other case was reported by Freer, in the *Journal of the American Medical Association*, March 30, 1901. There is no doubt that other tumors of this nature, in which the diagnosis was not verified by operation and microscopical examination, have been observed, but a very thorough search of the literature failed to reveal the report of any other case (with the exception of Freer's) like the author's.

I may mention in passing, in order to show the rarity of this form of benign intratracheal growth, that Bruns,[1] up to 1898, had collected altogether ninety-one cases of benign tumors occurring in the trachea, and of these only seven were cases of intratracheal struma. Since then two others, those of Baurowics and of Freer, have been reported, making nine only on record.

There have been, of course, a considerable number of accessory thyroid glands and thyroid tumors reported, occurring in more or less remote

* Presented to the Section on Laryngology, New York Academy of Medicine, January 22, 1902.

situations, viz.: the cases of intrathoracic struma, those that are substernal in position and connected directly with the thyroid gland, the accessory thyroid tumors at the base of the tongue, the parathyroid glands found in the upper third of the anterior surface of each lobe of the thyroid, which Gley has found in almost all animals, and some in still other parts of the air passages. (Osler,[10] Gruber,[11] Gley,[12] Warren,[13] Schadle,[14] Virchow, Wolf,[15] Butlin,[16] and others.) These cases are only mentioned here because they are of some interest in connection with the subject under discussion.

The history of the writer's case, which in some respects differs from any of the other recorded cases, is as follows:

Mrs. M. R., aged thirty-two years, was referred to me by Dr. J. B. Harvie, of Troy, N. Y. Her father died of some kidney trouble at the age of thirty-three years; her mother is living and well. Her two brothers and two sisters are living. One sister, it is interesting to note, has a goitre of considerable size. One sister and brother died in childhood. She had the usual diseases of childhood, but otherwise has always been well. Her menstruation commenced at the age of fourteen. She has always been regular, but has usually had considerable pain the first two days of each period. Her last menstruation was in June, 1901. She is now five months pregnant, and has two children, both of whom are living and in good health. About seven years ago the patient noticed a contraction of the muscles of the left side of the neck, and that the glands on the same side were swollen. Three weeks later she first noticed a difficulty in breathing, which was increased by the least exertion. The dyspnœa, which had irregularly but steadily increased, particularly during her present pregnancy, finally became so alarming that she was sent to the Troy Hospital, November 12, 1901, by her physician, Dr. Harvie. I saw her, with Dr. Harvie, on the following day for the first time. She was breathing with considerable difficulty, and there was some cyanosis of the lips.

On examining the neck a goitre of moderate size was found, the left lobe of the thyroid being somewhat, and the isthmus decidedly, enlarged. There was a marked inspiratory stridor, and on palpation over the upper part of the trachea a decided inspiratory thrill could be felt, a symptom that appears to be pathognomonic of high tracheal stenosis. No other enlarged glands in the neck were found. The examination of the lungs was negative, with the exception of a somewhat prolonged expiratory murmur at the left apex. Other organs normal. An examination of the nose, nasopharynx, pharynx and larynx, showed normal conditions.

On laryngoscopic examination, however, a tumor of considerable size, springing from the posterior and left lateral walls of the trachea, almost completely filling its lumen, was seen during deep inspiration. (Fig. 1.) The growth appeared to extend from about the first tracheal ring downward along the posterior wall. The tumor was regular in outline, and covered with a perfectly smooth, normal-looking mucous membrane. Several vessels were seen running over its surface.

During the next few days iodide of potash was given, 30 grains every three hours. The dyspnœa, however, becoming more serious every

day, an operation was considered imperative, and was performed November 16th.

Under ether, with the patient's head low, an incision extending from the lower margin of the thyroid cartilage to a short distance above the episternal notch was made. On account of the enlarged isthmus which covered the parts it was not considered wise to attempt to perform a preliminary low tracheotomy. The isthmus was found to be much enlarged, making the exposure of the trachea difficult. At this time the patient's breathing became very bad, and a high tracheotomy was performed, the isthmus being pushed down as much as possible. In cutting through the tracheal wall a small incision was accidentally made in the tumor, causing a most troublesome hemorrhage, which was finally controlled with a sterile solution of adrenalin chloride, 1 : 1000. The thyroid isthmus was then firmly ligated on both sides with catgut, and divided. The trachea being now thoroughly exposed a low tracheotomy was performed, the upper tube taken out, and the tracheal rings above the tube were split, as was also the cricoid. The tumor, which

FIG. 1.

was over 5 cm. long, extended from the first tracheal ring downward along the posterior wall, and almost filled the tracheal lumen. It was resilient to the touch, and was found to be firmly attached, by a very broad base, to the posterior and left lateral walls of the trachea, from which it could not be separated. It was, in fact, part of the tracheal wall. As much of the growth as possible was removed with snare and curette, the adrenalin solution being used continuously, on account of the severe and troublesome hemorrhage.

Because of the hemorrhage, and because the patient's condition was not entirely satisfactory, attempts to separate the portion of the tumor that remained from its attachment to the posterior wall had to be finally abandoned. The trachea was brought together with catgut sutures, the external wound being closed by a continuous subcutaneous silkworm-gut suture. A gauze tampon was inserted above the tracheotomy tube to prevent blood from oozing down.

Patient's condition was very satisfactory for several days after the operation, but on the fourth day her temperature, which had been nearly normal, suddenly went up to 102° F., and she developed a

double pneumonia. Nitroglycerin was administered, at first $\frac{1}{60}$ grain every hour by mouth, with $\frac{1}{30}$ grain of strychnine every three hours hypodermically. Whiskey was also given every hour. On the following night, November 21st, patient was in a very dangerous state, several times being in a condition of extreme collapse. Hypodermic injections of 5 minims of a 1 per cent. solution of nitroglycerin every twenty minutes during the collapse were each time followed by the most marked results, the pulse improving in quality within a few minutes after each hypodermic.

The next morning, November 22d, the patient again collapsed, respiration almost ceasing. It was evident that the trachea below the tube was filled up. The tube was taken out, the patient held over the side of the bed with the head very low, and with a long, narrow curved forceps I was finally able to remove from low down in the trachea several masses of almost solid mucus which nearly filled its lumen, and which she could not have expelled through the tube. The patient's breathing improved at once, and from this time on she steadily improved. For nearly two weeks, however, from the onset of the pneumonia her heart acted badly, the pulse being rather irregular, not of good quality, and never getting below 120. During this time nitroglycerin was administered continuously at hour intervals, with strychnine $\frac{1}{30}$ grain hypodermically every four hours. The nitroglycerin had to be stopped at times for part of a day when the patient complained too much of throbbing and pain in the head, and digitalis was given instead, but I would like to mention at this time that I do not believe there is any doubt that the large amount of nitroglycerin the patient received, and particularly the large doses given hypodermically during collapse, saved her life. She was discharged from the hospital in excellent condition on the twenty-ninth day after the operation, still wearing the tracheotomy tube. She was at that time about six months pregnant.

The portions of the growth removed were sent to Dr. Blumer for examination, who reported as follows:

BENDER HYGIENIC LABORATORY,
ALBANY, N. Y., December 21, 1901.

I enclose report on the tumor from the interior of the trachea:

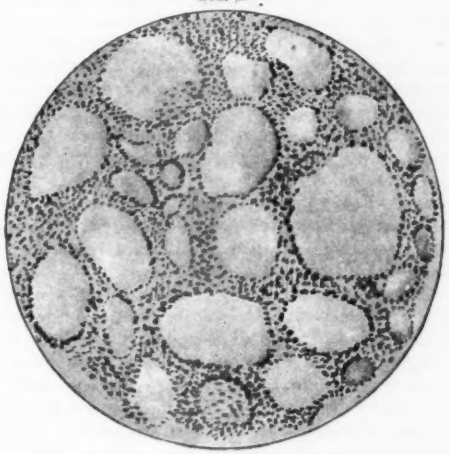
The specimen submitted consists of ten small fragments of growth, averaging half a centimetre in diameter. The tissue is pinkish in color and somewhat translucent. Microscopical examination shows that covering the growth on one side is normal tracheal epithelium. Beneath this is submucosa, but tracheal glands are not present in the section, and presumably lie behind the tumor. The tumor itself is made up of tissue which may be described in brief as exaggerated thyroid tissue. The alveoli are in arrangement exactly similar to normal thyroid, and consist of spaces lined by cubical epithelium and containing quantities of colloid. They differ from normal thyroid in the great variation in size and shape of the alveoli. (Fig. 2.) The amount of connective tissue between the alveoli is about that normally seen in the thyroid gland. The connective tissue contains a large number of bloodvessels.

Diagnosis. Colloid struma, originating in thyroid tissue situated beneath the submucosa of the trachea. GEORGE BLUMER.

It was not considered safe to permanently take out the tracheotomy tube until after her confinement, on account of the danger of a sudden swelling of the part of the tumor that had to be left. When the last laryngeal examination was made I found that this remnant had contracted considerably, so that she breathed without difficulty when the tracheotomy tube was temporarily removed, and I have no doubt that after she is confined it will almost disappear.

The origin of intralaryngeal and tracheal thyroid tumors was up to the time of Paltauf's investigations one of the most interesting enigmas in medicine, and for its solution it will be necessary to briefly review the reported cases.

FIG. 2.



Drawing of section; low power.

CASE I.—(Ziemssen's,[1] 1875.) The patient, a shoemaker, aged thirty years, developed laryngeal dyspnœa during the latter part of October, 1875, which rapidly increased. He had a goitre of moderate size. A tracheotomy was performed for the relief of the dyspnœa. Death on the following day of erysipelas developing in the wound. At the autopsy a tumor was found in the larynx, left side, which extended from the middle of the cricoid cartilage, and was about 2 cm. long and 1 cm. thick. It had a perfectly smooth surface and an intact mucous membrane. Microscopical examination disclosed that the tumor was made up of thyroid tissue, and, also, that the goitre had penetrated on the left side, between the cricoid and thyroid cartilages, into the lower part of the larynx.

CASE II.—(Reported by Bruns.[2]) The patient, a male, aged thirty-two years, had had since his seventeenth year difficulty in breathing, which had gradually increased. Examination of the neck showed a slight enlargement of both lobes of the thyroid. On laryngeal exam-

ination a tumor was seen in the lower part of the larynx, almost filling its lumen, and springing from the right lateral wall and part of the posterior wall. Operation, laryngo-tracheotomy. Growth extended from the fourth tracheal ring upward to close under the right vocal cord. On microscopical examination it was found to consist of thyroid tissue, with slight colloid degeneration.

CASE III.—(Heise-Bruns,[3] 1877.) Case of a girl, aged fifteen years, who for three years had had difficulty in breathing. Lateral lobes of the thyroid were not enlarged, but the isthmus could be felt as a node as large as a cherry. On laryngeal examination a subglottic tumor was seen on the posterior and right lateral walls of the larynx, slightly nodular, and covered with intact mucous membrane, taking up two-thirds of the lower laryngeal cavity. Operation, laryngo-tracheotomy. The tumor was found to extend from the second tracheal ring to close under the glottis, and had a very broad base. On microscopical examination it was found to consist of thyroid tissue.

CASE IV.—(Heise;[4] also from the Tübingen clinic, 1885.) The patient, a male, aged twenty-six years, had had slight dyspnœa after exertion, since his twenty-fourth year, which gradually got worse. The thyroid was not enlarged. Laryngeal examination, followed by tracheotomy, showed the presence of a tumor, 5 cm. long, extending from the first tracheal ring downward along the posterior tracheal wall. On microscopical examination the tumor was found to be made up of thyroid substance, showing slight colloid degeneration.

CASE V.—(Roth's.[5] Reported by Bruns, 1888.) Case of a woman, aged forty years. At the autopsy a small tumor, covered with mucous membrane, was found under the cricoid cartilage. On microscopical examination it was found to consist of small follicles with fatty degenerated epithelium.

CASE VI.—Paltauf's,[6] 1892.) A young woman, aged twenty-nine years, was brought to Albert's clinic, in Vienna, on account of alarming dyspnœa, and an immediate tracheotomy was performed. Four weeks before difficulty in breathing had developed, and became alarming three days before the operation. Examination of the neck showed the presence of a struma of moderate size. On laryngeal examination several red tumors were seen under the vocal cords, nearly closing the laryngeal lumen. Three weeks after the operation a large abscess of the left thyroid lobe developed, death resulting a week later. At the autopsy a small tumor was found, extending from the lower border of the thyroid cartilage to the cricoid cartilage. Microscopical examination showed this to be typical thyroid tissue.

CASE VII.—(Bruns',[7] 1898.) Case of a girl, aged twenty-four years, who had a small median goitre. On laryngeal examination a tumor was seen on the anterior wall of the lower laryngeal cavity and upper part of the trachea. Operation, laryngo-tracheotomy. An adhesion of the isthmus to the trachea was found, and *directly opposite* in the trachea the tumor was situated. On microscopical examination it was found to be a struma colloides.

CASE VIII.—(Baurowics',[8] 1898.) Case of a girl, aged twenty-one years, who had had an operation for tracheotomy. Under the left vocal cord a tumor was seen attached to the left lateral and posterior walls, filling the lumen of the lower laryngeal cavity, and extending down to the fourth tracheal ring. Operation, laryngotomy. On microscopical

examination the growth was found to consist of thyroid tissue, with slight colloid degeneration.

Case IX. (Freer's,[8] 1901.)—This patient, a woman aged thirty-two years, had a thickening of the mucous membrane below the cords, forming a ledge which projected into the laryngeal lumen around its whole circumference. This thickening extended down the trachea to the third or fourth ring, forming a prominent tumor on the posterior wall. On examination of the neck the thyroid could be felt. A tracheotomy was performed on account of a sudden subglottic swelling. Portions of the intratracheal growth were afterward removed through the tracheal wound, and were found to be made up of thyroid tissue. An operation for the removal of the growth itself was not performed.

Doubtful cases. Radestock's[17] case was formerly included under this head. In his case a tumor was found low down in the trachea, at the entrance to the main bronchus, closing its lumen entirely. Since the publication of his case it has been claimed by Paltauf and Kolisko[18] that it was not a true case of intratracheal struma, but that the microscopical examinations proved it to be a case of adenoma. Radestock's case was undoubtedly similar to the one reported by Scheuer[19] in 1893. Scheuer's case also turned out to be a true adenoma on the posterior wall of the trachea, extending from the sixth to the eighth rings. The other doubtful case was reported by Ball.[20] In this there was a tumor filling the upper part of the larynx and complicating a goitre. The laryngeal tumor was probably malignant, although Semon was of the opinion that it might have consisted of hypertrophied thyroid tissue. Mayer's case,[21] in which there was a struma nodule on the right wall of the trachea which had grown through the wall from a large struma, was also proved to be a malignant adenoma. For the reasons given, and because the clinical data were insufficient, Radestock and Ball's cases were not included in the above table. The statement made by Freer that his case is the *tenth* case on record is then *not* correct. His was the *ninth*. He also stated that five cases have been reported from Bruns' clinic. Only *four* have been reported from the Tübingen clinic, two by Bruns and two by Heise.

The two theories as to the origin of this most interesting form of tumor that have received the most consideration are those of Bruns and Paltauf. Bruns and Heise,[2] the chief exponents of the embryonal theory, held that in *intra-uterine* life a small accessory thyroid lobule from aberrant embryonic rudiments of the thyroid gland (Angeborene Verlagerung von Schilddrüsengewebe), must have, in such cases, been present in the fœtal larynx or trachea. This lobule, developing about the time of puberty, resulted in the true intralaryngeal or tracheal "accessory thyroid tumor." Paltauf[6] was able to prove in his case, by microscopical examinations, that this theory was not tenable. In his case there was a connection between the intratracheal growth and the thyroid gland externally. The thyroid was so firmly attached to the cricoid cartilage and upper three tracheal rings that it could not be separated from them. The space between the cricoid and first tracheal ring, and a portion of the external lateral lobe of the thyroid, which

was firmly adherent to the cartilage at this point, were examined microscopically, and he was able to prove positively that the thyroid tissue had penetrated (through the interstitial membranes) to the perichondrium and submucosa on the inner surface of the trachea, the cartilage itself remaining intact. So it is not necessary, as Heise thought, that in order for the thyroid tissue to penetrate into the trachea there must be a perforation, or at least a defect in the tracheal wall. Ziemssen,[1] too, observed that the struma had penetrated the lower cavity of the larynx between the cricoid and thyroid cartilages, and Baurowics was able to demonstrate the same origin of the intratracheal growth in his case. This observation of Paltauf's is the first instance on record of normal thyroid gland tissue penetrating to the interior of the larynx and trachea, although Orth,[22] in his *Pathological Anatomy*, makes the statement, "that strumas, but particularly the *malignant* neoplasms, could penetrate into the air passages, *i. e.*, into the larynx."

The only way that this penetration of normal thyroid tissue in Paltauf's case can be explained is by the intense adhesion of the right and left lateral thyroid lobes to the upper tracheal rings and cricoid. They were really part of the tracheal wall. This probably took place during fœtal development, although the thyroid tissue in all probability did not penetrate into the larynx until during extra-uterine life, and at a time when enlargements of the thyroid commonly take place—the period of puberty.

Paltauf's conclusions, that these intralaryngeal and tracheal tumors springing from thyroid tissue do *not* owe their origin to an intra-uterine deposit of thyroid tissue are of great interest. They should therefore *not* be called *accessory* thyroid tumors. They originate in extra-uterine life by penetration of the gland tissue between the cricoid and thyroid cartilages, between the cricoid and first tracheal ring, between the upper tracheal rings, and through the interstitial tracheal membrane itself, *from without*. When this occurs it should be considered as a direct extension of an enlarged thyroid gland—a parenchymatous struma. Proof of this assertion is that the thyroid gland has really grown fast to the cricoid cartilage, interstitial membranes, and upper tracheal rings. This abnormal adhesion can neither be explained by pressure, nor by an inflammatory process, but can only have occurred during the formation and development of the thyroid gland, and only in the way that the *fœtal* gland, in these cases, must be united with the perichondrium of the cartilage and the interstitial membranes.

Gruber's[11] investigations, perhaps, would give additional support to Paltauf's theory. He found, after examinations of many Russians and Bohemians, that there was often an accessory or really an extra lobule extending downward from the lowest posterior margin of the lateral lobes and lying very close to the trachea. These extra lobules may

also lie in the crico-thyroid space. The only parallel cases that possibly give some support to Bruns' theory are those observed by Streckeisen.[23] He found on sections through the hyoid bone seven times the so-called glandulæ intrahyoidea, that is, thyroid tissue was shut in the bone. He believes that this was shut in during the ossification period.

In my own case it could not be determined during the operation whether the left lateral thyroid lobe, which was enlarged, was adherent to the trachea or not. The isthmus was not, because in ligating it the ligatures could be readily passed between it and the trachea. It is a rational deduction, however, from the fact that the intratracheal growth was really part of the tracheal wall, and springing as it did from the posterior and left lateral wall, that in this case, too, the intratracheal tumor was really an offshoot from the left lateral thyroid lobe.

An analysis of the ten cases of this rare condition brings out a number of interesting points: (*a*) The location of the tumors in all the cases, with the exception of Bruns' last case, was characteristic. They were all situated in the lower part of the larynx and upper part of the trachea and attached to the lateral and posterior walls. Bruns' last case was the only exception to this rule, the growth being attached to the anterior wall. (*b*) This point decides another interesting fact before mentioned, that these tumors, for this reason, should not be called *accessory* thyroid tumors, because they are really offshoots from the thyroid, as proved in the majority of the cases by the adhesion of the thyroid to the tracheal wall, and in Paltauf's case, microscopically, by the infiltration of the interstitial membranes with the follicles of the thyroid gland. (*c*) They were all observed early in life, from the fifteenth to the thirty-third year, with the exception of Roth's case (the fortieth year). (*d*) A goitre of moderate size was present in all except in one of Heise's and in Freer's case. (*e*) They occurred in both sexes—three in males, and seven (including the author's) in girls and young adult women. A special consideration of my own case reveals some additional interesting points: It is the only case of which I could find any record in which the intratracheal struma was present in a pregnant woman; it is the second case on record in which the struma was confined to the trachea, extending from the first ring downward, the other case being one of Heise's. It is one of the largest, if not *the* largest recorded intratracheal tumor of this kind, extending as it did down the posterior tracheal wall for a distance of over 5 cm., or nearly two inches. The fact that it was present in a pregnant woman suggests another rather interesting connection between the intratracheal struma and pregnancy. I do not think there is much doubt that the pregnant condition had a great influence on the development and increase in size of both the extratracheal and intratracheal struma, because the dyspnœa was not nearly

so great before she became pregnant. It is well known that the thyroid frequently enlarges during pregnancy to cope with the increased metabolic changes of that period. Freund,[24] in his classical article on the relations between the thyroid gland and the female genital organs, brings out the fact that the gland is frequently enlarged in pregnant women, and that it almost always increases markedly in size during the birth of the child. This was true in forty-five out of fifty women examined by him. Tait[25] found an enlargement of the thyroid body in twenty women who had borne children. In his cases the increase in size developed during the latter months of pregnancy, and subsided very much after delivery. Wölfler[26] has shown that in the normal thyroid gland embryonic masses of thyroid cells are found here and there, particularly toward the periphery of the gland, and these, under certain stimuli, take on a kind of normal growth. Such a change occurs during pregnancy.

PROGNOSIS. The prognosis, on the whole, may be said to be favorable. Tumors of this nature, when completely removed, do not appear to have a tendency to recur.

TREATMENT. When the growth is large enough to seriously interfere with respiration a laryngo-tracheotomy for its removal should be performed as soon as possible, on account of the peculiar capacity tumors of this kind have for increasing very suddenly in size. I could not find any record of internal thyroid medication being used for intratracheal struma, but should think that it might be of value in certain cases.

CONCLUSIONS. 1. Cases of intratracheal struma are, perhaps, not so rare as the few cases on record would indicate. If laryngeal and, as far as possible, *tracheal* examinations of all cases of goitre were made, particularly when the thyroid is only *slightly* enlarged and the dyspnœa is severe, more cases would probably be discovered.

2. The term *accessory*, when applied to such tumors, is *not* correct, because they really are "off-shoots" of the thyroid gland.

3. Pregnancy, as in the writer's case, undoubtedly has a great influence on the development of the intratracheal struma.

I wish to take this opportunity to express my thanks to Dr. Harvie for his valuable assistance at the operation, and also to my clinical assistant, Dr. Fairweather, for so carefully following out the after-treatment of the case.

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EXENCEPHALIC (INIENCEPHALIC?) MONSTER WITH BILATERAL HARELIP AND CLEFT PALATE.[1]

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The monster which I wish to present this evening is a seven months' white female fœtus which was stillborn, being the first child of an extremely neurasthenic woman of seventeen and a half years, whose family history I cannot obtain, but whose pregnancy up to the time of the miscarriage was uneventful. The father is about twenty-five years of age, healthy and robust, but having a strong family history of tuberculosis, his father having died of phthisis, and his mother is now suffering with the same disease.

About one week before the miscarriage the mother fell directly forward upon her abdomen, followed by severe lumbar pain and uterine

[1] Read at the meeting of the Philadelphia Pathological Society, held February 13, 1902.

hemorrhage, but continued to feel fœtal movements up to within two days of the birth. Hydramnios was not present, as has been frequently reported in cases of this malformation, and labor was not long or severe.

Following the classification of Isidore Geoffroy Saint Hiliaire, whose work upon teratology has practically been accepted and followed by all writers upon this subject, this monster belongs in the general class of exencephalus, which is described as "characterized by a malformed brain situated at least in part without the cranial cavity, the bony walls of which are themselves imperfect." This general class is further subdivided into (1) the notencephalus, in which the cranial contents are in large part without the skull, resting upon the back of the neck, the tumor protruding through a fissure or aperture in the occipital bone. This deformity is usually associated with hydrocephalus of greater or less degree; (2) proencephalus, in which the same deformity as just described exists upon the anterior portion of the skull; (3) podencephalus, and (4) hyperencephalus, in these the cranial deformity is upon the vertex and the tumor protrudes from above. The podencephalus differing from the hyperencephalus only in degree; (5) iniencephalus, in this subclass the deformity of the skull is the same as in notencephalus, with the addition of a spinal cleft of varying degree; in some cases the failure of union extends as far downward as the coccyx, leaving the spinal canal open throughout its entire length. In this class lordosis and compensatory kyphosis are common—the head is tilted strongly backward, causing the face to look almost directly upward, which, with the faulty development of the vault of the cranium and apparent, rather than real, protrusion of the eyes, has suggested the term "frog-faced" monster, although this term is not exclusively applied to the iniencephalic subclass.

In 1896 Dr. H. F. Lewis presented a specimen of this monstrosity to the Chicago Pathological Society, and at the same time collected all the recorded cases which, with two other specimens, he described at the same time and which had not previously been recorded, brought the total number to twenty-five. I have been able since that time to find the report of only four other cases, although the search through the records has been cursory rather than exhaustive.

No mention could be found in any of the recorded cases of an associated harelip or cleft palate (unless the case described by Dr. Wood could be looked upon as an attempt at harelip formation), with the exception of a single sketch in Ahlfeld's *Atlas* which quite closely resembles the photograph of the present specimen.

The present specimen is an under-developed female fœtus; skin and visible mucous membranes normal. The neck is entirely absent, the malformed head being placed directly upon the upper portion of the thorax in such a position as to turn the face directly upward, so that

the plane of the face is at a right angle to the plane of the body, and to cause the deformed or under-developed occipital bone to rest directly back upon the anteriorly curved cervical vertebræ (Figs. 1 and 3).

FIG. 1.

The general appearance of the monster. The match-stick (*a*) has been passed into the opening in the malformed brain cavity; (*b*) the remains of the brain, meninges, and fringes of skin rolled up as a ball; (*c*) area over which there was failure of development of true skin. The constriction about the upper portion of the thorax and the arm was produced by a tight string used to suspend the fœtus in the preserving fluid.

FIG. 2.

Photograph of monster, showing the characteristic formation of the face, and in addition the bilateral harelip, with the greatly protruding intermaxillary bone. The two white spots seen just below the centre of the tongue were caused by moisture on the lip at the time the photograph was taken.

The entire upper portion of the skull above an imaginary plane beginning on a level with the superciliary ridges and passing backward

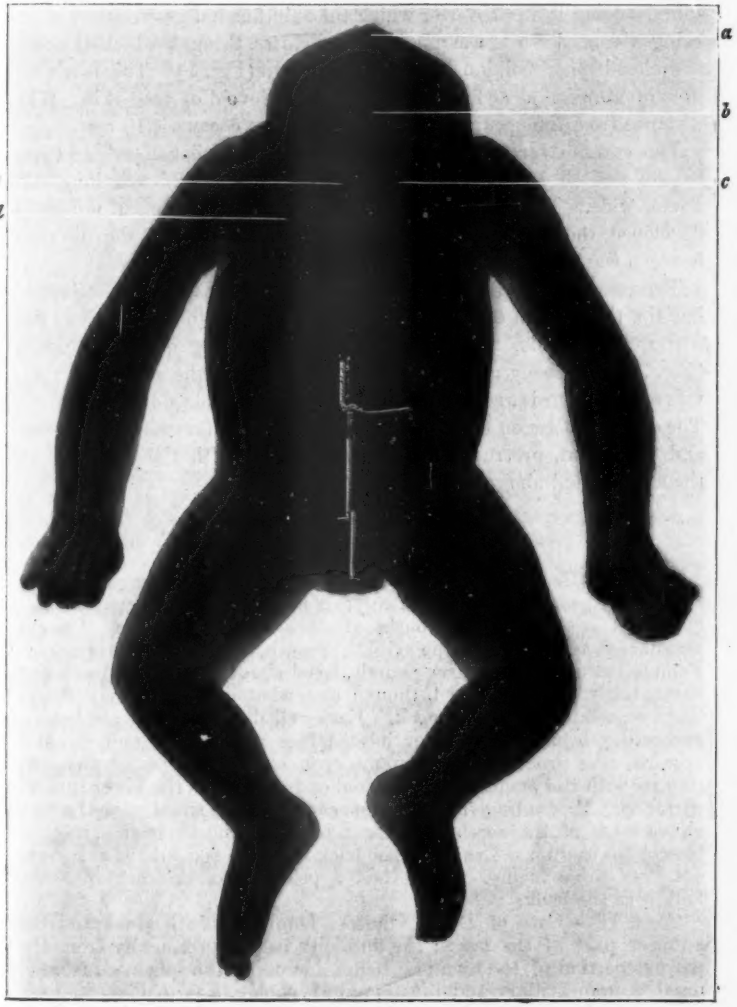
FIG. 3.

"X-ray" photograph, showing (*a*) the characteristic cervical lordosis. The remains of the brain and meninges appear as the faint shadows surrounding the optical bones (*b*).

at a right angle to the plane of the face is entirely absent and replaced by a solid bony plate covered by hairy skin. At the junction of the

occipital bones and spinal column is an opening into the skull large enough to admit the end of one's little finger (in the photograph is shown a match-stick passed into the opening), from the margins of this open-

FIG. 4.



"X-ray" photograph, showing (*a*) the protruding intermaxillary bone; (*b*) failure of union of hard palate; (*c c*) abnormal position of malformed and separated optical bones; (*d*) scapula and scoliosis.

ing are extending the brain membranes and remains of the brain, together with fringes of skin (in the photograph these are seen rolled up as a ball).

Extending over the back from the opening into the skull to the lower lumbar vertebræ and laterally about 2.5 cm. to each side of the spinal column is an area over which the skin has not grown, the tissues being absent down to the muscular structures, through which the ribs and closed spinal column can be plainly seen (Fig. 1). This is not an area of abrasion as at first appears, but one devoid of true skin. The distance from the opening into the skull to the coccyx is 10 cm.

The ears, so far as can be seen, are normally developed, and are behind and slightly below the shoulders. They are 2.5 cm. long and 1 cm. wide. The eyes are normally located and appear normally developed, the palpebral fissure measuring 1.5 cm. and the distance between the inner canthi is 1.5 cm.

The mouth, which is 2 cm. wide, is the seat of a well-marked bilateral harelip, the cleft on each side extending well up into the nostril of the corresponding side, the intermaxillary bone being quite prominent (Fig. 2). The bony cleft extends backward into the mouth and involves both hard and soft palate to a considerable degree (Fig. 4). The distance between the alæ nasi is 1.5 cm. The tongue is quite large and prominent, protruding from the mouth. With the exception of the above-noted abnormalities the fœtus is normal.

Synopsis of Collected Cases.

Case I.—(Case of Dr. Albert C. Bowerman.) Patient, aged twenty-four years, gave birth, about two years ago, to an apparently normal child, but it died in ten months of some cerebral trouble. Present pregnancy advanced to the eighth month. Hydramnios present. Female fœtus, weighed three pounds, lived about one hour. Body and limbs fairly well developed, though somewhat disproportionate, lower limbs especially long. No neck. Ears well developed and are behind and rather below the shoulder joints; face well formed and directed upward, eyes prominent. Cranium open in occipital region and continuous with the unclosed spinal canal as far down as the lower lumbar vertebræ. Protruding from the upper end of this canal were the congested lobes of the cerebellum much enlarged and exposed across the base of the sacrum. Length of the back from the occiput to the sacrum not over three inches. Child had appearance of crescent with the hollow at the back.

Case II.—(Case of Dr. B. Onuf.) Duplicity of the face and the anterior part of the head; the duplicity begins proximally from the petrous portion of the temporal bones, including the sphenoid, frontal, nasal, supramaxillary and inframaxillary bones. Two pharynges are present which communicate with each other. Craniorrhachischisis involves the entire vertebral column.

There is the interposition of a peculiar os sacrum-like vertebral

formation, and two longitudinal bones (each divided into anterior and posterior portion) between the occipital and temporal bones of each side. In the proximo-distal direction these intercalary formations form the transition between the bones of the skull and the vertebra. There is also absence of the bony sacrum.

CASE III.—(Case of Dr. W. Atkinson Wood.) Mother, aged twenty-three years; father, aged twenty-six years. Female fœtus born dead, but the tissues appeared healthy and fresh. Entire scalp from the superciliary ridge to the position of the occipital protuberance and from one mastoid region to the other was a mass of dry gangrene studded with pear-shaped fibrous outgrowths. Both eyes protruded markedly, and the mouth in the mid-line was quite absent, being represented by two lateral slits into which a probe passed easily for half an inch. Both ears were well developed. At the third or fourth lumbar vertebra was a myelocele. The lower extremities were fully flexed at the hips, so that the feet which were in the position of talipes spasticus, or dorsalis, were fitted and pressed accurately under the position of the chin.

The vertex was removed on a level with the superciliary ridge, and the bones were so fused together as to appear as one bony mass. The petrous portion of the temporal bone and mastoid bones were fused into one mass; on the inner side of this mass were two cavities containing brain matter, each about the size of a bean. In the substance of these bony masses the ossicles were well developed. The sphenoidal cells were well developed, and the nasal chambers connected directly with the anterior fossa of the skull.

The vertebral column had no direct communication with the skull, being kept in apposition only by skin and connective tissue. The spinal canal opened directly at the depression on the posterior part of the skull, the spinal cord being thus exposed to the air.

The pharynx and larynx were well developed. Tongue and tonsils were contained in a membranous sac on the anterior surface of the spinal vertebræ. The internal carotid was doubtfully developed (which the author ascribed as the probable cause of the cranial deformity).

The lower and upper jaws were ankylosed together; the buccal cavity was divided into two lateral halves. The alveolar processes of the upper jaw were fused with the hard palate, leaving a slit-like opening between.

CASE IV.—(Case of Dr. Barton C. Hirst.) The doctor presented a photograph of the monster, with no description.

The specimen shown this evening will be presented to the Wistar Institute of the University of Pennsylvania.

I am indebted to Dr. Clifford B. Farr for the translations of the foreign references, and to Dr. Thomas S. Stewart, who furnished the "X-ray" negatives.

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A CASE OF HYPERNEPHROMA OF THE KIDNEY COMPLICATING PREGNANCY.

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AND
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The following case of tumor of the kidney appears to deserve mention both because of the rarity of the tumor and the peculiar manner in which it manifested itself.

Mrs. T., a negress, aged thirty years, was admitted as an emergency case to the Medico-Chirurgical Maternity Hospital, on November 3, 1900. Examination of the patient on admission showed her to be about six months pregnant. She complained of pain over the uterus, and an internal examination showed evidence of a threatened miscarriage. More interesting than the pregnancy was the presence of a tumor which could be felt at the lower border of the liver. Dulness over this tumor extended into the right flank.

We were unable to elicit any previous history throwing light upon its origin. The patient was anæmic, but had not the characteristic cachexia of malignancy. The urinalysis was negative, the temperature elevated. Five days after admission she spontaneously miscarried, giving birth to a six months' fœtus. After delivery the tumor stood out more prominently and appeared to be rapidly increasing in size.

A tentative diagnosis of either abscess of the liver or a large growth of the kidney was made. The tumor had not the feel of a cystic kidney, nor were the clinical symptoms suggestive of liver abscess. She still continued to have fever and was rapidly growing worse, and on November 17th was etherized and an exploratory incision made. The tumor occupied more of the region of the liver, and upon deep palpation fluctuation was noticed.

An incision was made over the most prominent portion of the growth through to the peritoneal cavity. What was then found was supposed to be a retroperitoneal abscess, so gauze was packed around the wound to shut off the general peritoneal cavity, and an incision was made into this bulging mass. A large quantity of thin, dark, very offensive fluid escaped. It had the odor of urine. As the patient was now in an extremely critical condition, a large drainage-tube was inserted. The abscess was drained, and the next day the patient seemed a trifle improved, but she commenced to lose ground again, and died December 17th, a month and a half after her admission to the hospital.

Autopsy Notes. December 19, 1900. Body of a much emaciated young colored woman of middle stature, about thirty years of age. The face bears an expression of suffering. Rigor mortis is absent. Inspection of the body shows an open wound in the right hypochondrium, large enough to admit a finger, and communicating with some part of the intestine, forming a fecal fistula. The edges of the wound are indurated, the surface necrotic and foul. In addition to this intestinal fistula, there is a sinus which descends deeply toward the right

side of the abdomen and communicates with what appears to be an abscess cavity, as puriform matter bathes the exploring finger. When closely examined, this matter was curdy and much resembled the pus of a cold abscess. The body was opened by suitable incisions.

Thorax. Pericardium normal; pleural adhesions on both sides. Heart: brown atrophy. No valvular lesions. Aorta normal, except for beginning atheroma. Lungs: slight congestive œdema.

Abdomen. Chronic peritonitis chiefly localized about the area of disease on the right side. Recent peritonitis near the external wound. Spleen, small; capsule thickened, substance indurated, vessels large. Adrenals apparently normal. Left kidney normal in size and appearance. On section, mild parenchymatous changes of the cortex. Ureter normal. Right kidney (see below). Ureter normal. Bladder normal. Uterus: enlarged puerperal uterus. No sign of any pathological condition. Ovaries normal. Pancreas normal, except for inflammatory adhesions to the surrounding viscera. Stomach and duodenum normal. Small intestine normal. Large intestine, operation fistula communicating with the transverse colon. The transverse and ascending colon are adherent to surrounding structures by inflammatory adhesions. Vermiform appendix normal and free of adhesions. Liver normal. Gall-bladder normal. Nervous system not examined.

The only lesion of interest or importance is to be found in the *right kidney* and its contiguous structures.

The sinus descending from the external wound was found to communicate with a cavity above and internal to the right kidney. The appearances suggested that this cavity had once been large, but had collapsed where the external wound was made. It seemed to arise either from the kidney or the retroperitoneal tissues. The kidney together with the surrounding peritoneal tissue, forming the entire walls of the somewhat indefinite sac of the abscess (?), were removed and carefully dissected. The ureter and pelvis of the kidney were now found to be normal. Little by little the kidney was dissected free from the surrounding cellular tissue, which was thickened and infiltrated until gradually the lower three-fourths were exposed, after which it was split longitudinally along the convex surface. The substance of the organ was now found to be free from disease—a condition which was entirely compatible with the fact that no abnormal condition of the urine was discovered during life.

Tracing down the sinus from above and laying it open, it was discovered that the inner surface of its wrinkled and contracted wall was thickly studded with more or less rounded nodules, suggesting some neoplasm. These became larger as the upper part of the kidney was approached. In the superior, external, and posterior portion of the kidney there was a rounded excavation about as large as a walnut. In this excavation lay a neoplasm nearly as large as the excavation itself, and projecting so as to form a rounded mass from the bottom of the excavation into the sinus. The color of this neoplasm, as well as the color of the nodules in the neighborhood, was grayish-yellow, the surface smooth, the consistency rather firm and somewhat friable.

A section passing through the neoplasm and the adjacent kidney substance showed the tumor to be sharply demarcated from the kidney substance, being separated by a band of fibrous tissue.

The presence of the neoplasm in the kidney, the numerous nodules

in the sinus, and the absence of evidences of any inflammatory process, beyond that depending upon the operation fistula, entirely changed the aspect of the case.

It now appeared as if the condition was one of primary neoplasm of the kidney with enlargement and softening. The puriform matter that escaped when the operation was performed, and continued to escape subsequently, was the softened contents of the neoplasm enclosed in its capsule of perirenal tissue. The escape of this softened tissue was followed by collapse of the sac and the necrosis of the remaining part of the growth with the formation of the rounded eminences found in the walls of the sinus.

Concerning the nature of the growth the naked-eye appearances are not clear. It undoubtedly arises from the kidney, yet its growth away

FIG. 1.

Hypernephroma of the kidney. Organ split longitudinally, and showing the tumor in the upper left-hand half.

from the kidney substance and its sharp demarcation from it are peculiar. The growth shows no disposition to infiltrate neighboring organs or tissues, and has given no metastases. These facts seem to warrant the assumption that the growth is a *hypernephroma—i. e.*, a growth developing from a fragment of the suprarenal body included within the kidney tissue during the embryonal differentiation of the tissues.

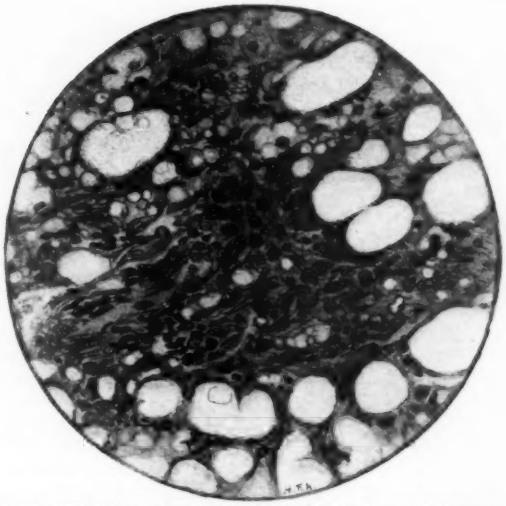
Microscopy. The fragments of tissue were hardened in formaldehyde, embedded in paraffin, and stained for study by various methods.

Three difficulties immediately presented themselves and made the determination of the nature of the growth difficult. First, the entire growth was in a condition of advanced retrogressive change; second, it was evidently distinctly modified by the acute and chronic inflammatory processes that had taken place in and about it; and, lastly, it was a peculiar, atypical growth.

Beginning the examination with that part of the growth which is attached to the kidney and occupies the cavity in its upper portion, we find, though the largest tumor mass is firmly attached to the kidney, it does not blend with its substance anywhere, but that between the tumor tissue and the kidney tissues there is a fairly sharp line of circumscription, consisting in part of a fibrous tissue belonging to the tumor and in part of fibrous tissue resulting from atrophy of the parenchymatous elements of the organ.

The kidney structure is quite normal until the described line of demarcation is reached, when a sudden and complete pressure atrophy is observed. From the study of sections of this kind it becomes evident that the growth has not taken place from the kidney tissues.

FIG. 2.



Hypernephroma of the kidney, showing the indefinite structure and the presence of considerable fat. This section passed through the centre of the main tumor nodule. (Zeiss, Ocular II., Objective D D.)

The tissue forming the tumor is very largely in an advanced condition of *fatty infiltration*. This is true not only of that part in contact with the kidney, but also of the remote parts. So wide-spread is this infiltration that it becomes impossible to decide upon the nature of the cells, nearly every one of which is involved in the process. Among the fatty globules thus formed and thickly distributed in the trabeculæ of fibrocellular structure, and about large bloodvessels which are present, there are cells of various kinds, most of which are unfortunately altered by degenerative changes:

1. *The proper cells of the tumor.* These cells are rather large, for the most part irregularly ovoid, and mononucleated. They are closely packed together, without any arrangement, the cytoplasm is universally injured by retrogressive changes and prone to contain vacuoles and

granules. The nuclei were originally round, large, and vesicular, but almost every variation from the normal presents itself. There are fragmented nuclei, vacuolated nuclei, and giant pale nuclei. Occasionally a large cell with several nuclei is observed. In general the cells bear more distinct resemblance to sarcoma cells than those of any other type, yet the extensive fatty metamorphosis and the original scanty amount of chromatin are distinctly contrary to this view.

2. *Connective-tissue cells.* Spindle cells, derived from the stroma of the tumor and from the bloodvessels are very numerous. Indeed, certain areas consist almost exclusively of them, their large size, arrangement in bundles, etc., forming an embryonal tissue closely suggesting spindle-cell sarcoma. These areas are, however, not numerous, and proximity to the trabeculæ, etc., from which the cells are derived, usually sufficiently explains them. Spindle cells, endothelial cells, and irregular cells evidently derived from the connective tissue and bloodvessels are scattered irregularly throughout the growth and often mingle with its proper cells.

3. *Plasma cells.* There seem to be a good many of these scattered about among the tumor cells, but their numbers are greatest in the areas in which the connective-tissue cells predominate.

4. *Leucocytes.* Leucocytes occur in small numbers throughout the tumor. They are most numerous in the connective-tissue areas surrounding the bloodvessels.

There is no regular framework of connective tissue supporting the cells of the tumor.

The bloodvessels are numerous, large vascular trunks more numerous in proportion than the capillaries.

Degeneration. In addition to the wide-spread fatty infiltration of all parts of the growth there were numerous areas of necrosis in which no definite structure was any longer visible. Here and there, and especially in the connective-tissue areas, pigmentation of leucocytes and connective-tissue cells with hemosiderin was observed, but nowhere in the growth were hemorrhages found.

When other nodules of the neoplasm, from the wall of the sinus and from the perirenal tissue, were examined the advanced fatty infiltration of the cells was the most marked feature. In nearly all of these fragments the retrogressive changes were so marked that the cellular structure could not be studied.

It is evident, therefore, that the histological structure of this tumor conforms to no regular tumor type. It is a growth attached to the right kidney and partly embedded in a fossa in the organ, yet developing from some other structure and not invading the kidney. Its peculiar cells are subject to fatty infiltration. The tendency of the growth is to increase in size without metastatic distribution and without infiltrating contiguous structures. All of these facts seem to point to its development from abnormal tissue. It did not grow from the right adrenal itself, however, as that organ was found normally placed and reasonably normal. Therefore if of adrenal tissue it must have been from a "rest" or fragment misplaced and in apposition with the kidney. The preservation adopted did not permit us to determine the presence or absence of glycogen, but the facts already given, and especially the marked fatty infiltration, lead us to believe that the tumor was correctly called *hypernephroma.*

OBSERVATIONS UPON RECENT METHODS OF TREATING CORNEAL ULCERS, WITH ESPECIAL REFERENCE TO THE USE OF CARBOLIC ACID AS A NOT INFREQUENT SUBSTITUTE FOR THE ACTUAL CAUTERY.

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The general and more definite recognition of the important rôle which micro-organisms play in the etiology of corneal ulcers has led, as might be supposed, to decided changes in the therapeutic measures employed in the treatment of this often troublesome condition, and, it may be added, to modified views as to the beneficial action of some of the older and well-tried remedies.

In the text-books upon eye diseases of twenty years ago we find but scant reference to bacteria as factors in the causation of conjunctival or corneal inflammations, and practically nothing as to the employment of bactericidal agents, as such, in their treatment. Then, as now, nitrate of silver was used in purulent conjunctivitis, and, at Gayet's and Fuchs' suggestion, the actual cautery was beginning to be employed in the more dangerous types of corneal ulcers; but the good effects of the former were ascribed to its "astringent and caustic" action, and of the latter, by one authority, at least, to its supposed influence in reducing intra-ocular tension.[1]

At the present day, while it is conceded that the efficaciousness of nitrate of silver is in part due to its direct action upon the conjunctival inflammation, it is in larger measure attributed to its bactericidal properties, and especially to its power of penetration, which enables it to reach and destroy the gonococci that have found lodgement beneath the superficial layers of the conjunctival epithelium, as well as those that are free in the conjunctival sac. And, in like manner, as to the actual cautery in the treatment of corneal ulcers, its good effects are now ascribed mainly to its powerful antiseptic action, as was first pointed out by Sattler.[2]

At the period referred to, if, in spite of atropia, warm fomentations and a pressure bandage, a corneal ulcer continued to progress and threatened the integrity of the eye, reliance was placed chiefly in paracentesis of the anterior chamber, in incision through the base of the ulcer (Saemisch), or in the performance of an iridectomy. Now, when

[1] Diseases of the Eye, Soelberg Wells, 1883, p. 233.
[2] Transactions of the Fifteenth Annual Meeting of the Heidelberg Ophthalmological Society, 1883, p. 104.

a threatening ulcer of the cornea is encountered, one asks what exceptionally virulent micro-organism is causing the unfavorable condition, and by what means it can be eradicated and the ulcer rendered aseptic, or, on the other hand, if the micro-organism be not of exceptional virulence, what has lowered the resisting power of the corneal cells, or of the phagocytes whose function it is to assist in their defence, and how it can be brought up to its normal standard. So, while such drugs as atropine, eserine, and the more recently introduced holocaine are still employed in the treatment of ulcerative processes of the cornea, and are held to be of undoubted value, germicidal agents, such as the actual cautery, carbolic acid, tincture of iodine, formalin, chlorine water, iodoform, and boric acid, and the mechanical removal of the bacteria and the corneal tissue which they have invaded by curetting, are regarded as of the first importance.

And this brings me to the matter which chiefly induced the writing of this paper, namely, to speak of the good results which, in my own hands and in the hands of several of my colleagues, have been obtained from the use of carbolic acid in the treatment of threatening ulcers of the cornea—the application of the pure acid to the ulcer for its germicidal effect and, in large measure, as a substitute for the actual cautery. It is, perhaps, hardly necessary for me to say that this use of carbolic acid is not novel, and that I am fully aware that others have employed it in the same manner and with favorable results.

I must confess that I have not been one of those who, upon small provocation, are disposed to use the actual cautery for the control of corneal ulcers, and that my inclination has been to employ, instead, some more easily managed and less dangerous procedure; and this has been not merely because I am aware that the application of the actual cautery to the cornea has been known to cause permanent opacity of the lens, and must almost invariably leave an indelible leucoma of the cornea, nor because I have had occasion to observe how easily it may lead to an unintentional opening of the anterior chamber, but, rather, because I feel that whenever it is possible for the surgeon to substitute a simpler and safer surgical procedure for one that is less simple and less safe it is his duty to do so, provided, of course, it is equally efficacious.

That the application of carbolic acid to a corneal ulcer *is* a simpler and safer procedure than its cauterization by the galvano- or thermo-cautery goes without saying. But what of its efficacy? I am not prepared to assert that it will accomplish in every case what the cautery will do, or that it should wholly supplant the latter; but I believe that in many cases in which it is usual to employ the cautery carbolic acid may be substituted with advantage, and that in most cases

it is judicious, at least, to make trial of it before resorting to thermal cauterization.

In applying pure carbolic acid to the cornea it is, of course, important to limit its action carefully to the affected part. To facilitate this the eye should be anæsthetized by cocaine, which renders the procedure entirely painless. I have found it convenient to make the application by means of a pointed toothpick, about the tip of which a very small quantity of absorbent cotton has been wound. If much cotton is used an excess of the acid will be taken up, and it will be almost impossible to prevent its spreading over healthy portions of the cornea. To the surface of the ulcer the acid should be thoroughly applied by a gentle rubbing movement, which is, in effect, a sort of curettage. When the ulcer is foul and its walls are lined by infected and necrotic material, this should be removed with a small curette before the acid is applied. When, however, this condition is less pronounced, aided by the loosening action of the cocaine, the cleaning of the ulcer may be effected satisfactorily by means of the toothpick, armed with a wisp of dry cotton. After the acid has been allowed to remain in contact with the ulcer for a few moments, the lids meantime having been held apart, its further action should be arrested by flushing the cornea with sterile water, normal salt solution, or a saturated solution of boric acid. After the effect of the cocaine has passed off some smarting or discomfort may be felt in the eye, but usually this is not pronounced.

The effect of carbolic acid upon the surface of the cornea is rather startling, for it attacks the epithelium energetically, and in an instant renders it opaque, causing it to assume a milky appearance. Bowman's membrane, it would seem, is much more capable of resisting its caustic action, for the superficial opacity which it produces quickly disappears.

It seems hardly necessary, and yet it is, perhaps, best, to say that the employment of carbolic acid in the manner described is not to be regarded as part of the routine treatment of corneal ulcers; on the contrary, the cases in which it is called for are distinctly the exception and not the rule. When the ulcer is the product of infection with one of the less virulent bacteria, such as the staphylococcus aureus—as is commonly the case in phlyctenular keratitis—the yellow oxide of mercury, supplemented, perhaps, by boric acid, commonly meets the condition most satisfactorily. It is the dangerous ulcers—the serpiginous ulcer, the ulcer complicated by hypopyon—which are commonly due to the presence of the pneumococcus and less frequently to the more virulent streptococcus, that call for the energetic germicidal action of carbolic acid and in which its good effects are manifested.

I shall not prolong this paper with detailed accounts of cases in which

the efficacy of carbolic acid has been shown; but, in justification of the views I have expressed as to its value, will simply mention that I have employed it with gratifying results in hypopyon ulcers (in the early stages, especially), in suppurating ulcers of traumatic origin following oyster-shell injuries, etc., and in dendritic keratitis, and that recently one of my colleagues, Dr. James Bordley, applied it to a threatening corneal ulcer complicating gonorrhœal conjunctivitis, and which, it seems probable, was due to a secondary infection, with the result that the rapid progress of the ulcer was at once arrested and the process of repair quickly established.

In conclusion, and to prevent possible misapprehension, I wish to add that while in what has gone before I have dwelt upon the importance of using energetic antiseptic agents in the treatment of the more dangerous types of corneal ulcers, I am far from holding that they should be our sole reliance, that they should be employed to the exclusion of other remedies. Atropine, holocaine and, exceptionally, eserine and opium, as a lotion to be applied over the closed lids, are as useful to-day in controlling suppurative and ulcerative processes of the cornea as they ever were, and the same may be said of the liberal administration of quinine, which, unquestionably, augments the resisting power of the cornea, and so may determine, as we would wish it, the outcome of the combat between the invading bacteria and the phagocytes which hasten, literally as well as metaphorically, to their circumvention.

PRIMARY SYPHILITIC OPTIC NEURITIS.*

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of Philadelphia.

Primary syphilitic optic neuritis is an affection so rare that its existence is even denied by some authors. Thus Hock[1] refers to syphilitic neuritis only as a symptom of cerebral syphilis. Hughlings Jackson[2] does not believe that primary syphilitic optic neuritis exists, but that neuritis manifests itself always as a result of cerebral gumma.

Undoubtedly, syphilitic inflammation of the optic nerve manifests itself most frequently in the form of papillitis resulting from some form of cerebral syphilis; but certainly in a number of rare instances the nerve itself seems to be primarily affected by the syphilitic poison.

* Read before the Section on Ophthalmology of the College of Physicians of Philadelphia, April 15, 1902

Leber[3] makes a distinction between the papillitis arising in consequence of a cerebral gumma and the true syphilitic optic neuritis appearing primarily in the trunk of the optic nerve. Foerster[4] and Alexander[5] also believe in the existence of a primary syphilitic neuritis, the latter stating that he has studied two such cases. Horner[6] and Knorre[7] have found upon pathological examination of such cases that there is sometimes marked inflammatory thickening in both optic nerves from the optic foramen to the chiasm, and even beyond. Ole Bull[8] has observed hyperæmia and opacity of the optic nerve and surrounding retina in the early stages of syphilis, but believes that marked papillitis is to be found in the later stages of the disease. Januskiewicz[9] states that he has seen a case of primary specific optic neuritis two and a half months after infection. Horstmann,[10] in a most excellent paper upon the subject, from which the writer has quoted quite freely, believes in the existence of a primary syphilitic optic neuritis, and reports eight cases of this condition. In his cases all the patients had suffered from syphilis and had undergone specific treatment for a shorter or longer period. The ophthalmoscopic examination revealed in each some swelling of the optic disk, which encroached but little upon the surrounding retina. In some of the cases the papillitis was monolateral, and in those cases in which both nerves were affected one side was usually much worse than the other. There was hyperæmia, together, with more or less opacity, as is ordinarily found in a moderate degree of papillitis. In all the cases there was found concentric contraction of the visual fields, but in none was a central defect observed. The author concludes, therefore, that the condition could not have been due to descending neuritis, and, moreover, there was no evidence of any existing orbital or cerebral disease. In addition, in all of the cases the disease was either removed or improved by the administration of anti-syphilitic remedies.

In this same class the writer is inclined to believe the two following cases belong:

Mr. ——, aged forty-five years, was referred to me for an examination of his eyes on November 5, 1901, complaining of an aching pain in and immediately behind the eyeballs, and an inability to see well, especially with the left eye. Vision had been growing less acute for two weeks, and for a few days prior to the examination of his eyes it had become rapidly diminished in the left. Vision of the right eye equalled 6/9; of the left 1/100. There was a history of occasional attacks of headache, always preceded, as the patient expressed himself, by "shooting stars," that it is believed were migrainous in character, and which had existed for a long time, and still exist.

The pupillary reactions were normal. An ophthalmoscopical examination showed that both media were clear; there was a moderate

papillitis with very little involvement of the surrounding retina, and with but little exudate showing on the surfaces of the disks. There were no hemorrhages in either eye, and in the left the papillitis was much more marked than in the right, the latter disk presenting only slight veiling of the margin.

The patient acknowledged the initial lesion of syphilis three months before the eye examination was made, and this statement was corroborated by the physician who had him under treatment at this time. There were present mucous patches and a moderate eruption of the skin, and he had been taking mercury irregularly.

The field of vision for the right eye showed concentric contraction for both form and colors, but no scotoma could be detected. The vision of the left eye was so reduced that the patient could not distinguish large test objects, but with a candle flame the limit was also found to be concentrically contracted.

The patient was immediately placed upon mercurial inunctions and rapidly increasing doses of potassium iodide, and in one week showed a moderate degree of improvement. In two months' time the neuritis had entirely subsided, and the vision in the right eye equalled 6/5, and in the left 6/7.5, the fields being normal. Thirteen days after the examination was made of this patient he brought his wife in to see me, who presented the following history:

Mrs. ——, aged forty-three years, had been complaining for a few weeks of inability to see well, together with some pain in and behind the eyeballs. She had always worn glasses of her own selection, obtained from an optician. The vision of the right eye equalled 6/7.5 —, and of the left 6/7.5 —. Both pupils reacted promptly to light, convergence, and in accommodation.

The ophthalmoscopical examination revealed in the right eye an oval disk with its edges very slightly veiled, but no other changes. In the left eye there was distinct papillitis, the nasal edge being most affected, with but little involvement of the surrounding retina. No hemorrhages were found.

The interesting history was ascertained that the patient was also syphilitic, presenting mucous patches and a skin eruption, and that the initial lesion was acquired from her husband, whose primary lesion had been acquired only three and a half months before. During this period, like her husband, she had been using mercury irregularly. The field of vision for the left eye was concentrically contracted in a moderate degree; the field of the right eye was not affected. She was at once placed upon mercurial inunctions and rapidly increasing doses of potassium iodide, and in six weeks' time the papillitis had almost entirely subsided, and the patient's vision equalled 6/5 — in each eye, with normal visual fields.

It seems to the writer that these two cases of papillitis, occurring so early after the initial lesion of syphilis, and the circumstances attending the same, must be placed in the class in which the optic nerve is primarily affected. There was no history of any cerebral complication, and it hardly seems probable there could have been any such condition without corresponding symptoms. In addition, the early appear-

ance of the papillitis, within two and a half months after the appearance of the initial lesion in patients, would seem to exclude cerebral disease, as pointed out by Horstmann. The concentric contraction of the visual field would seem to argue against the extension of the inflammatory process from the sheath to the substance of the optic nerve. It is certainly a most unusual and interesting fact that the husband acquired the initial lesion of syphilis, inoculated his wife, and that both presented papillitis within three months from the beginning of the disease, the left nerve being principally affected in each case.

The manner of the production of primary syphilitic papillitis is not definitely determined, but may possibly be brought about by syphilitic disease of the central vessels. The very fortunate result obtained in the above two cases is believed to have been brought about because they came under observation very early after the beginning of the disease, as it has been shown that when primary syphilitic neuritis occurs in a patient whose infection dates back more than a year the prospect of complete recovery is small.

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REVIEWS.

THE PRACTICE OF OBSTETRICS, BY AMERICAN AUTHORS. Edited by CHARLES JEWETT, M.D., Professor of Obstetrics and Gynecology in the Long Island College Hospital, New York. Second edition, revised and enlarged. 8vo., pp. 776. New York and Philadelphia: Lea Brothers & Co., 1901.

THIS composite work appears in its second edition, with changes in its contributors and with increased and revised contents.

The character of the articles and their assignment are scarcely consistent with the title of the volume. In a book whose title would indicate that it is devoted entirely to a description of the practice of obstetrics the first 100 pages are given to anatomy, physiology, and embryology. In contrast to this the section upon Obstetric Surgery is allotted but 87 pages. In the distribution of articles the immediate repair of lacerations of the generative tract, the induction of abortion and premature labor, the delivery of the retained and adherent placenta, Cæsarean section, the Porro operation, symphysiotomy, and the subject of ectopic gestation are assigned to gentlemen whose titles and practice inform us that they are interested in gynecology only. In view of the fact that there are in the United States a number of competent obstetric surgeons who have had abundant experience in these subjects, and whose records have been published, it is remarkable that none of them was selected to write upon these topics. The inconsistency displayed in the arrangement and management of topics and the title of the volume call attention to this as a composite book, a type of publication largely created for commercial interest. In arranging for such a volume, publishers select as large a number of writers as possible connected with teaching institutions, thus insuring a sale for the book. Scientific consistency and a uniform standard of excellence may be sacrificed by this arrangement. While composite volumes contain many articles of permanent value, they must be encyclopædic in scope, or are, we think, inferior to a consistent treatise by one writer, experienced in all topics of the subject upon which he writes.

Medical education has now advanced to the point where anatomy, physiology, and embryology are subjects for study in the early years of a medical course. They receive their best consideration in separate text-books, and the best literature of modern times will not find it necessary to begin a volume with an anatomical or physiological or embryological epitome which has little scientific value. A purely practical consideration of obstetrics would certainly have given a greater space to obstetric surgery than to anatomy, physiology, and embryology, and the practitioner depending for guidance upon such a volume desires the experience of one accomplished in Cæsarean section and the other operations of obstetric surgery.

While we thus take issue with some important features of the book, and believe it more a trade book than a scientific volume, we have no intention of slighting the work of its accomplished editor and many articles contained in the volume. While we may differ with some of the methods of treatment advised, and while our methods of study may be slightly different in some respects, we have nothing but admiration for the papers of Dr. Edgar, Dr. Williams, and the contributions to the volume from its editor, from Dr. Dickinson, and others associated with him. The diagnosis of pregnancy has received no better exposition than that given by Dr. Dickinson, enriched by excellent illustrations. For the general practitioner, the keystone of the obstetric arch is the management of normal labor, and this receives full and adequate exposition at the hands of Dr. Jewett. Dr. Robb indulges in reminiscences of his medical career before he became a specialist in gynecology by writing upon the puerperal state and its management, while the care of the newborn child is assigned to Dr. Bartley, who gives an excellent résumé of artificial infant feeding. We recognize the sound surgical judgment of an old friend in Dr. Henrotin's article upon ectopic gestation, while Dr. Cameron and Dr. Webster contribute an interesting section in that portion of the volume devoted to the pathology of labor. Among the best expositions of eclampsia, its causation and treatment, which we have seen is Dr. Edgar's article, in which he describes with abundant illustrations his method of rapidly dilating the cervix to secure prompt delivery.

Dr. Williams' paper upon puerperal infection is an authoritative monograph upon the subject to which practitioners and teachers as well may refer with profit. In discussing the treatment of puerperal septic infection attention is properly called to the value of strychnine and alcohol. The uselessness of sublimate injections to secure deep penetration of the tissues is clearly shown, and the danger of intra-uterine douches of antiseptics, and especially of bichloride of mercury, receives ample consideration. It is urged that bacteriological examination of the lochia and of the interior of the uterus be made whenever possible. If streptococci are found, then local treatment of the uterus is of little value, while if the germs of putrid infection are present, thorough douching with sterile salt solution is indicated. The uterus must be made to contract, if necessary, by the use of ergot. Antipyretic drugs should not be given, but excessive fever should be treated by the use of cold. As regards surgical interference, pus-tubes not adherent may be removed through the abdominal wall, while if extensive adhesions are present they should be punctured and evacuated through the vagina, with subsequent packing of the abscess cavity with gauze. Hysterectomy for puerperal sepsis has a very restricted field.

In the section upon Obstetric Surgery the repair of recent lacerations of the vagina and vulva are illustrated with some very good drawings. The immediate repair of the lacerated cervix is considered permissible and as affording a fair chance for success. In the induction of abortion and premature labor several obsolete methods are given, and also those which have received the sanction of wide experience. In cases where the uterus must be promptly emptied in early pregnancy dilatation and curetting are very properly advised as the method to be preferred. In cases of adherent placenta the advice is given to try faithfully Crede's method first, and then to remove the placenta by the

hand, douching the uterus with normal salt solution afterward. In the use of forceps the indications and dangers are clearly stated, and the operation of forceps delivery is recognized as attended with difficulty and danger. Although the advice is given to sterilize the forceps by boiling, there is no mention made of a portable and convenient sterilizer in which this may be done. A basin of bichloride solution and one or two squares of cheese-cloth comprise the instrumental armamentarium for antisepsis. The use of sterile glycerin or vaseline is advised as a lubricant for hands and instruments. We have in creolin and lysol lubricant antiseptics which, in our experience, should be employed for boiling the forceps and as lubricants in all manipulations. It is possible that the illustrations do not clearly represent the practice of the writer, for the forceps blades are shown guarded but by the tips of the fingers and pushed in by the thumb and other hand. The writer prefers to remove the forceps when the head is on the pelvic floor so low down that it can be expelled by light pressure through the perineum. We are glad to know that the introduction of the finger into the rectum is thought inconsistent with aseptic precautions. Various devices are shown for making axis traction with the hands and with several forms of instruments. In the treatment of occipitoposterior rotation attention is called to a manipulation often neglected, the rotation of the entire body of the fœtus anteriorly. Under full anæsthesia this is often successful and is accompanied by anterior rotation of the occiput. It is so safe and valuable a procedure that it should not be neglected.

In treating of Cæsarean section the writer takes what we believe to be the proper stand, that the limit of the operation has been advanced through perfection in technique. We cannot agree that the better method consists in keeping the uterus within the abdomen, for the disadvantages claimed by turning out the womb are more than compensated for by the better control of hemorrhage and the removal of all uterine fluids from the abdominal cavity. The uterus is emptied much more rapidly and easily when turned out of the abdomen than if it be retained. The rubber ligature is seldom necessary if an intelligent assistant be available. In closing the womb the majority of experienced operators prefer silk, and as the uterus must contract in involution, a permanent suture is especially desirable. The manner of dressing a patient who has had a Cæsarean section is of considerable importance. The writer refers to a suitable bandage, by which we infer that the many-tailed flannel bandage commonly used after abdominal section is advised. In our experience in difficult cases, where a patient is very restless after operation, or where the patient coughs or vomits, this bandage is inefficient. We have seen the best results by covering the abdomen completely with strips of adhesive plaster encircling two-thirds of the body. In this manner an absolutely firm and unyielding support is given to the abdominal wall during coughing or straining. It seems to us that the writer gives, in a book addressed to general practitioners and intended to describe the practice of obstetrics by physicians, dangerous advice as regards the choice of time for Cæsarean section. It is said that it is not necessary to wait until labor pains come on nor for marked dilatation of the cervix. The surgeon may sometimes be compelled to operate during labor. Experience has shown that pelvimetry, palpation, and the estimation of the size of the fœtus are not in all cases reliable guides for the performance of the Cæsarean

operation. The test of labor must be awaited in many of these cases. The majority of obstetricians, we think, agree in stating that the patient should come into labor and should have sufficient uterine contractions to determine by actual test whether the head can or cannot enter the pelvic brim. If it does not under favorable conditions and the patient under close observation, then operation must be immediately performed. There are some notable instances where surgeons have announced Cæsarean operations for a given time, and summoned an audience, to have the patient disappoint them by spontaneous delivery. The Cæsarean section is an operation rarely practised by a gynecologist, belonging, as it does, to the obstetrician, or in emergency to the general surgeon. Experience has taught the obstetrician that only the test of labor justifies so important a decision, and the surgeon in this regard may profit by obstetric experience.

The treatment of the Porro operation is unsatisfactory because cœliohysterectomy with intraperitoneal treatment of the stump is included under the head of the Porro operation. Under the heading of Cæsarean Section the excellent advice is given that if the uterus has been infected before the operation the whole organ should be removed. Under the paragraph upon the Porro operation it is stated that this method of procedure has been superseded by hysterectomy. These statements place the Porro operation in its proper light, namely, as a wellnigh obsolete surgical procedure. It would have been better had the writer described complete removal of the uterus and cœliohysterectomy, as both are logical and satisfactory operations, and both are now performed in place of the Porro operation. Considerable space is given to symphysiotomy, and the method by direct incision, as practised by Farabeuf, and Ayers' subcutaneous method are described. We have had satisfactory results in eight cases by the subcutaneous method as originally practised, and have obtained excellent apposition by immobilizing the pelvis with a single broad strip of adhesive plaster.

We cannot close a review of this volume without again calling attention to the excellent work of its editor. It is our regret that he did not write more of the volume, and that the requirements of publication should have hampered him in the arrangement and choice of the contents of the volume.

The book is clearly printed, and most of the illustrations are clear and good. Some of the colored illustrations are not remarkable for excellence. The book contains a complete and efficient index.

E. P. D.

AN AMERICAN TEXT-BOOK OF PATHOLOGY. Edited by LUDVIG HEKTOEN, M.D., and DAVID RIESMAN, M.D. Illustrated. Philadelphia and London: W. B. Saunders & Co., 1901.

IN criticising an American text-book of pathology the reviewer must take into account the fact that the publishers claim that it is "the most representative treatise on the subject that has appeared in English," and that it is the outcome of the desire of the editors and publishers to place in the hands of the medical student and physician "a comprehensive text-book on the essential principles and facts in general pathology

and pathological anatomy." The question, of course, is to what extent the assertion is justified and the desire realized. As a representative text-book upon American pathology we should expect to find among the list of contributors to the volume the names of certain illustrious workers in this field. These, however, do not appear. It must not be supposed that the men who have contributed are incapable or unknown, but the omission of the others to whom we allude must be accounted a defect in the work. There is another feature in the book which we think merits criticism. It has been the custom for some time in German and American text-books to add to each section, either by way of a preface or appendix, a list of the more important articles which have been published on the subject treated, and this is particularly important in a text-book of pathology, a subject whose field is so vast that practically all men in it are specialists. In the present book, had the literature been added, and particularly the literature that has been contributed by American investigators, not only would the book have been improved, but a great service would have been done to American pathology; for perhaps because we are so prone to quote German authorities we know too little regarding the work of our colleagues in the United States. Another fault that, however, is not found in all the articles is a tendency to omit allusion to other authors or to quote authors without reference. In a subject as theoretical as is pathology, concerning the simplest facts of which there is at the present day so much discussion, it is not sufficient to know the opinion of any one man, no matter how authoritative his opinion may be; but we expect to be informed, at least in a general way, concerning the ideas of other workers, and some of the articles in which this fault is carried to extreme are more suitable for quiz compend than for a formal text-book of pathology, for they are a mere statement of the current teaching without any critical discussion of the subject. In other cases the author chiefly used in the preparation of the article is entirely too obvious, and as a result there is a lack of independence.

On the other hand, some of the articles are most admirably treated. Authorities are stated frequently, references are given, and the subject is treated in a scholarly and thorough manner. This is particularly true of the articles by the editors, of Dr. Collins' section on the pathology of the nervous system, and Dr. Beyea's article upon the female genital tract, although in the last two articles references are too frequently omitted. Among omissions, some of which are perhaps inevitable in the first edition of any text-book of this character, we may note the discussion of certain pathological cell-forms that are now exciting considerable interest in pathology. We refer particularly to the plasma cells, mast cells, to the significance of the eosinophile cells in tissues, to the different varieties of giant cells, etc. The discussion of the pathology of the lymph glands and spleen, which might have been more properly classified, is entirely more adequate. A more thorough account of the present status of the infectious theory of cancer would have been desirable, for although it cannot be said that we have reached any definite conclusions, the results of experiments have contributed largely to our knowledge of the subject of cancer and even to our knowledge in some other directions. The subject of pseudoleukæmia receives scant attention, particularly in view of the recent advance in the pathology of this disease. Some of the illustrations deserve

criticism. Many of them are borrowed; the sources are various, and this gives rise to more or less confusion in appearance. This is particularly true of the illustrations in the article upon bacteriology. It is always desirable, if possible, to have the illustrations in a text-book prepared according to some definite and uniform plan. It is almost supererogation to cite Ziegler's text-book as a model to be followed in this respect.

The book is well printed. The errors of proof-reading appear to have been singularly few, and an earnest and largely successful effort has been made by the editors and contributors to include the very latest knowledge upon each subject. J. S.

PROGRESSIVE MEDICINE, Vol. I., 1902. A Quarterly Digest of Advances, Discoveries, and Improvements in the Medical and Surgical Sciences. Edited by HOBART AMORY HARE, M.D., Professor of Therapeutics and Materia Medica in the Jefferson Medical College of Philadelphia. Octavo, 452 pages, 5 illustrations. Philadelphia and New York: Lea Brothers & Co.

THE first issue of *Progressive Medicine* for the current year reviews the literature of 1901 under the heading of Surgery of the Head, Neck, and Chest; Infectious Diseases; the Diseases of Children; Pathology; Laryngology and Rhinology, and Otology.

The division on Surgery, by Charles H. Frazier, the longest in the volume, covers 128 pages. Especially interesting is a very complete discussion of the advances in the surgery of the Gasserian ganglion and the fifth nerve, to which Dr. Frazier, in conjunction with Dr. William G. Spiller, has recently made a noteworthy contribution. The X-ray treatment of skin-cancers is a topic of timely interest, receiving due attention, while a section of fully ten pages is devoted to a very complete discussion of our present knowledge of enlargements of the thyroid gland, their pathology and their surgical treatment. Considerable space also is devoted to the recent literature of the surgical treatment of injuries and surgical diseases of the heart, pericardium, and large vessels, a branch of surgery which bids fair to achieve brilliant and, until lately, unhoped-for success.

The article on Infectious Diseases has been entrusted to Frederick A. Packard, who contributes seventy-seven pages, twenty-four of which are devoted to the year's literature upon typhoid fever. The complications of the disease, many of them of quite unusual occurrence, are very fully discussed. Four and a half pages are devoted to diphtheria, which fairly indicate the extent and importance of the most recent literature of this disease, upon which, until lately, so much has been written since the introduction of the serum treatment. Indeed, activity in work upon diphtheria apparently for the time has been exhausted, and there seems little more to be done for some time to come. Varicella, smallpox, measles, and dysentery together occupy nine pages, which sufficiently cover new points of interest. The section on Tuberculosis is mainly devoted to Koch's startling paper, read before the British Congress on Tuberculosis, and to Ravenel's somewhat contradictory conclusions on

the same subject. Important work upon the insect-borne diseases, yellow fever and malaria, receives notice, and short sections upon Influenza, especially its nervous complications, upon scarlet fever, and upon cerebro-spinal meningitis complete the review.

The Diseases of Children, by Floyd M. Crandall, occupying fifty-seven pages, is a significant indication of the activity of work in this increasingly important branch of medicine. Infant feeding, as usual, claims considerable attention, and the recent advances are well outlined in a section covering eight pages. The general acceptance of the percentage basis of feeding is clearly indicated in all the contributions to the subject, though the tendency to simplification of methods, and consequently less regard for accuracy, seems to be at present in favor. The rest of the article, which is divided according to the diseases of the various systems, adequately covers the new work of the past year. Passing mention may be made of the fact that, as shown in a discussion upon summer diarrhœas, the leading authorities of the country are very closely in accord as to the essential treatment of these diseases.

Pathology, reviewed by Ludvig Hektoen, in an article of eighty-seven pages, the second longest of the volume, is restricted to the original investigations in serum pathology, immunity, pathogenic micro-organisms, general pathological histology, and oncology. Lack of space forbids more than general mention of the vast amount of new work that is here very satisfactorily sketched, the number of references far exceeding those of any other division of the volume. Considerable space is devoted to the recent important studies of the etiology and pathology of cancer.

Laryngology and Rhinology are considered in an article of fifty-one pages, by St. Clair Thomson. Especially important is a very complete presentation of the general therapeutics of suprarenal extract and adrenalin, which have lately given promise of their value in throat and nose diseases.

The volume concludes with the section on Otology, by Robert L. Randolph. While naturally the shortest division of the six, it presents an adequate review of the progress of the year in this branch of medicine, especial mention being deserved for the sections on vibratory massage and upon the surgery of the mastoid.

Referring, in conclusion, to the volume as a whole, it may be said that the present issue of this very valuable periodical is fully up to the high standard maintained in the previous issues, and that it constitutes an indispensable adjunct to the working library of all who labor in the arduous field of advanced medical knowledge. T. S. W.

A Text-book of Diseases of Women. By Charles B. Penrose, M.D., Ph.D., formerly Professor of Gynecology in the University of Pennsylvania, Surgeon to the Gynecean Hospital, Philadelphia. Fourth edition, revised. Philadelphia and London: W. B. Saunders & Co., 1901.

The fourth edition of this book has many new features, both in the text and by the addition of instructive drawings, which place it in a still higher plane of excellence than before. For the student and the general practitioner it is especially trustworthy, dealing with each subject in a clear, concise manner, presenting the best teachings of

modern gynecology without the tedious rehash of antique methods, and outlining in the main only one mode of treatment, which is to the student a distinct advantage. The chapters on the diagnosis and repair of tears of the perineum and cervix are of especial value. These conditions are of so much importance that they deserve more attention than is ordinarily given to them in text-books on gynecology. Penrose's description of their appearance and their diagnostic features is excellent, while his outline of the operative treatment is rational and clear. The methods of Emmet have been carefully revised, and, while still followed in the main, many new points have been added, increasing their efficiency. In the chapter on "Prolapse of the Uterus" the author's treatment of the subject is most wise. It is very well described in the text, and a series of drawings showing the different steps of the operation for its relief elucidate it clearly. The pathological features of each condition and disease have received much more attention in this than in the previous editions of the book. The reason that this side of the work is perhaps not as complete as it might be is given by the author in his preface when he states that "he has, as a rule, omitted all facts of anatomy, physiology, and pathology which may be found in the general text-books on these subjects. In the chapter on "Cancer of the Uterus" cancer of the ovary has been added, and the insertion of new plates in this chapter makes it an excellent one. The withdrawal of many old plates and the substitution of new ones more clearly illustrating the admirable quality of the text would be wise, as some of the drawings are certainly not up to date.

The chapters on "Diseases of the Ovaries" have been carefully rewritten and improved, and a description of teratoma of the ovary has been added. Endothelioma of the ovary is also a useful addition to this chapter.

The chapter on "Diseases of the Urethra and Bladder," while not as full as it might be from the practitioner's stand-point, is nevertheless sufficiently adequate for the student.

The chapter on the "Technique of Gynecological Operations" has been brought well up to date, and very clearly and decisively written. The author's large and successful experience as an operator make it of great worth. The post-operative treatment of cases is somewhat old-fashioned.

In a few years the third edition of this book has been exhausted; that it has been very successful, and that its popularity is well deserved, is unquestioned. R. F. W.

MODERN OBSTETRICS, GENERAL AND OPERATIVE. By W. A. NEWMAN DORLAND, A.M., M.D. Second edition, revised and enlarged. Pp. 797. Philadelphia and London: W. B. Saunders & Co., 1901.

THIS is an enlarged edition of a manual of obstetrics originally designed to facilitate a review of the subject by students. The present book is a literary résumé of the subject in which a fair review up to the time of publication is given. The book contains little original matter, and is not enriched by the results of an extensive experience. In type and illustrations attention has been paid to economy at the expense of the volume. E. P. D.

PROGRESS

OF

MEDICAL SCIENCE.

MEDICINE.

UNDER THE CHARGE OF

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Diabetes and Pregnancy.—HERMAN (*Edinburgh Medical Journal*, February, 1902, p. 119) reports a case of pregnancy complicated by diabetes. The patient was a Jewess, aged thirty years. She had been married twelve years and had had seven children, the last three of which had been born dead. At about the third month of her eighth pregnancy she began to complain of weakness, pruritus, thirst, and emaciation. She had suffered from thirst during her previous pregnancies. She was informed by her physician about this time that she had diabetes. At about the seventh month she began to have uterine pains, associated with severe vomiting. She was admitted to the London Hospital in an almost moribund condition on March 26th. She was practically unconscious. The following day the membranes were ruptured, and she was later on delivered of a dead child weighing five and three-quarter pounds. The amniotic fluid was excessive. For the next few days the patient's condition varied markedly. She had rigors and fever, and gradually became weaker, and died on April 6th, but apparently not of diabetic coma. The urine averaged about 70 ounces daily. The amount of sugar ranged between 50 and 70 grammes. One examination failed to show any diacetic acid. The autopsy revealed that there was a round-celled sarcoma involving the right pleura. The right pleural cavity contained 2½ ounces of pus. The pancreas was not examined.

According to Herman, Matthews Duncan was the first to study the effects of diabetes and pregnancy on one another. Recently the subject has been carefully studied by Kleinwächter. According to the latter, two-thirds of the cases of diabetes in women do not begin until after the menopause. The disease is consequently infrequent as a complication of pregnancy, and when it does occur in a child-bearing woman it usually suppresses menstruation and

sometimes produces atrophy of the uterus. Our knowledge of the clinical history of this complication of pregnancy is based on but a few cases.

The symptoms of diabetes coming on during pregnancy may disappear within a short time after delivery, and recur again in subsequent pregnancies. This indicates that the pregnant condition favors the production of the disease. Statistics show that prognosis in these cases is more favorable than in those in which diabetic patients become pregnant. Some of the cases of pregnancy associated with intermittent diabetes have recovered from the latter after the period of child-bearing has ceased. When a diabetic woman becomes pregnant, however, the disease usually becomes aggravated and its progress hastened.

Premature delivery, due to intra-uterine death of the child, has occurred in about two-thirds of the published cases of pregnancy with diabetes. Hydramnios is rather frequent. The children have often been large. In two cases the liquor amnii contained 3 per cent. of sugar, and in one the fœtal urine contained sugar.

The question as to whether pregnancy should be interrupted or allowed to go on is apparently not yet a settled one among obstetricians. According to Herman, the early termination of pregnancy will prove the best treatment for a pregnant diabetic. If pregnancy be allowed to go on the following are the possibilities:

1. The chances are two to one that the child will die in utero. Its life is therefore not of much account.

2. It is possible that when the pregnancy is over the diabetes may get well. This is more likely to take place the earlier the pregnancy ends.

3. The patient may die from collapse and coma soon after delivery. This is more likely to occur the longer that pregnancy has gone on. One of these three events has occurred in most of the published cases; those in which pregnancy and labor were gone through with without influencing the diabetes or being influenced by it are in the minority.

Kleinwächter advises against premature delivery, on the ground that there is no evidence of its benefit. Apparently, however, it has only been induced once in the published cases, and then in a case in which the mother was moribund. As stated, Herman advises acting on probability and inducing premature delivery.

Apparent Contagion in Rheumatism Due to Meyer's Diplococcus.—ALLARIA (*Revista Critica di Clinica Medica*, 1901, vol. ii., p. 805) states that the remarkable observations of Meyer in Leyden's clinic have been reported in a previous number of this journal. This observer succeeded in cultivating a diplostreptococcus from the tonsils of five cases of acute rheumatism with angina. Bouillon cultures of this streptococcus produced characteristic polyarticular arthritis in rabbits. The exudates in the joints were usually serous, and sterile by ordinary culture methods. Meyer and Leyden both believe that this diplostreptococcus is the true specific agent of acute articular rheumatism.

Allaria, in Bozzolo's clinic, instituted control experiments, in the course of which he came across three cases of so remarkable a character as to merit publication. The first, a young woman, aged sixteen years, who had pre-

viously had several attacks of acute rheumatism, developed an acute tonsillitis, followed by a fresh attack of articular rheumatism lasting about four weeks. The sister of this patient, after nursing her, developed a similar attack, entering the hospital six days later. A friend of this patient, who had incipient pulmonary tuberculosis, and was in the hospital at the same time, developed also an acute tonsillitis after associating with the second case. Two days after the onset of the tonsillitis, acute rheumatism set in. A nurse, aged twenty-two years, who swabbed the throat of the first patient was seized with tonsillitis, followed by polyarticular rheumatism and high fever of a month's duration. Another nurse who took her place and attended the first two patients developed also tonsillitis, with polyarticular rheumatism; this was fortunately mild and without complications, though it kept her in bed for twenty-three days. Finally, a third nurse who followed this latter, although she took great precautions, developed severe tonsillitis, which lasted more than a week, and was associated with high fever. In all these cases the tonsillitis began violently with severe chills and rapid rise of temperature; the tonsils were much enlarged, although in two cases only were there slight traces of exudate. In the first three patients the bacteriological examinations of the throat were made. These showed streptococci, agreeing in all essential points and characteristics with those described by Meyer. A cubic centimetre of a forty-eight-hours' culture injected into guinea-pigs was followed by no clear reaction at the point of inoculation. The animals, however, gradually lost their vivacity, and four or five days after the injection painful swelling appeared in various joints, especially the tibiotarsal articulations of the posterior extremities. This swelling gradually disappeared, and the animals recovered. In those animals which were killed the fluid proved to be serous; there was subcutaneous œdema about the affected articulations, but no muscular infiltration. Under the microscope the exudate showed but few corpuscles and no micro-organisms, but on culture similar streptodiplococci were obtained.

In none of the animals used did exudates appear in the larger serous cavities. Cultures from the pleura, peritoneum, and heart's blood were negative.

A fourth case differed from the others in that the attacks were not preceded but followed by angina, and also in the greater virulence of the micro-organisms, which otherwise possessed characteristics similar to those of the preceding case. In this instance the control animals died rapidly with a general septicæmia. The author believes that while it is as yet impossible to assert positively with Meyer that this organism is the specific causal agent of acute rheumatism, yet if acute articular rheumatism is a true nosological entity and not a syndrome, as has been believed by some authors, there is much which would lead one to adopt this view.

Experimental Cholecystitis and Cholangitis of Auto-infectious Origin.—Ehret and Stolz (*Berliner klin. Wochenschrift*, 1902, vol. xxxix., p. 13) state that it has been shown that anything tending to diminish the motility of the gall-bladder and favor the accumulation of residual bile offers opportunity for the development of bacteria which otherwise do not flourish in the bile-passages. Especially is this true of the presence of foreign bodies

which hinder the entire expulsion of the bile from the gall-bladder. Ehret and Stolz have conducted a number of experiments to determine whether the injection of aseptic bodies into the gall-bladder or common duct might eventually be followed by the development of auto-infectious cholecystitis or cholangitis. In five cases the gall-bladders of dogs were filled with small hollow glass balls measuring about 10 to 13 millimetres in diameter. These had been carefully sterilized and broken at two points opposite one another. All the dogs recovered perfectly from the operation. One of the animals which was killed in two months showed a great abundance of bacteria in the gall-bladder. Three months after operation the dogs were placed under unfavorable conditions of diet. Severe diarrhœa followed in all four dogs. Two died of suppurative cholecystitis.

In six other instances small bits of absorbent cotton were introduced into the gall-bladder. Four of these dogs died after attacks of diarrhœa from eight to sixteen weeks after the operation. In all there was a suppurative cholangitis. In two in which laparotomy was done eight to ten weeks after the first operation the tampons were found in the common duct. The gall-bladders were greatly distended and showed an abundance of non-virulent bacteria. The bacteria varied in nature, being similar in the main to those which one finds in the normal bile of dogs when great quantities are used in the culture. They were essentially the same as those which appear after operations diminishing the motility of the gall-bladder, and also to those which usually entirely outgrow in bacteria which are introduced in attempts to develop an experimental cholecystitis. The spontaneous development of cholecystitis and cholangitis appeared to be favored by a temporary increase in virulence of the colon bacilli as a result of diarrhœa.

These observations are interesting in that they form an entire parallel experimentally with the conditions occurring clinically in cholelithiasis. The infection in these instances clearly occurred through the ducts.

A Case of Tuberculosis of the Skin following Accidental Inoculation with the Bovine Tubercle Bacillus.—RAVENEL (*University of Pennsylvania Medical Bulletin*, February, 1902, p. 453) reports a case of tuberculosis of the skin resulting from the infection of a wound during autopsies on two tuberculous cows. He has already reported three similar cases.

On July 27, 1901, Dr. G., while performing autopsies on two cows, the subjects of experimental tuberculosis, wounded the flexor surface of one of his wrists. By September 10th there was a nodule in the skin at the seat of the wound, measuring 15 by 8 mm. This was excised on September 14th. Portions were inoculated into two guinea-pigs, both of which developed generalized tuberculosis. Sections of the nodule showed the characteristic histological picture of the tubercle and also large numbers of typical tubercle bacilli.

Ravenel regards this case of great importance, considering Koch's opinion that human and bovine tuberculosis were different diseases and not intercommunicable. He says that such cases do not settle the entire question of the transmissibility of bovine tuberculosis to man, but that they prove most conclusively that the bovine germ finds soil and conditions in the tissues of man suitable for its multiplication.

SURGERY.

UNDER THE CHARGE OF

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Aneurism of the Mesenteric Arteries.—GALLIVARDIN (*Gaz. Hebdomadaire de Med. de Chir.*, 1901, No. 82) states that in studying the histories of cases of obliteration of the mesenteric arteries, which are composed nearly entirely of cases of embolus of the superior mesenteric artery, one is surprised not to encounter more frequently an infectious endocarditis as the origin of the embolic process. A recent monograph states that out of fifty-five cases of embolic obliteration of the vessels, the presence of an infectious endocarditis was only proven in four cases. The reason for this is that the septic emboli cause an alteration in the walls of the artery in which they may lodge, which tends to cause dilatation of that vessel, and so these cases are not reported as embolism but as aneurisms of the superior mesenteric artery. From the etiological point of view these aneurisms of the mesenteric artery should be considered in two groups: first, those of unknown origin, and second, those due to a septic embolus the result of an infectious endocarditis. Out of sixteen reported cases the author finds that seven should be considered in the first class, and of these in two cases there was a specific history, but in the other five cases the cause could not be determined. It is interesting to note that three of these five cases occurred in very young women, aged twenty, twenty-three, and twenty-four years, respectively. The remaining nine cases were the result of a septic embolus. The superior mesenteric artery was the site of the aneurism in nearly every case; a similar predominance is noted in the cases of embolism. Out of twenty-three reported cases, in only two cases was the inferior mesenteric artery affected. The aneurismal tumor is nearly always situated near the superior portion of the mesenteric artery, at the point where it penetrates the mesentery and gives off its first branches. The sac is rarely large, generally being about the size of a hen's egg. The sac may rupture in the folds of the mesentery or directly into the peritoneal cavity. The symptoms may be separated into two classes or periods: those of the evolution of the sac and the period of rupture. The symptoms of the first period, or that of evolution, vary much in different cases. The sac may occasion absolutely no symptoms, the patient being unaware of any abdominal lesion until the sac ruptures, as in the case reported by Lecadre. However, there usually exists some pain or other vague abdominal symptoms. In some cases the abdominal pains are so severe as to suggest the presence of an aneurism of the abdominal aorta. In only

four of the reported cases could the tumor be felt on palpation. In the last period the patient may die before the rupture of the sac from the extension of the causal endocarditis or as the result of some other intercurrent disease. However, rupture is a frequent termination of these cases. In all cases in which this happened death was not sudden, but soon followed after the appearance of abdominal symptoms, violent abdominal pain, and later nausea and vomiting. The patient has the facies abdominalis, is pale, and dies in a few hours. The same symptoms are caused by a rupture in the walls of the intestines in the region of the duodenum. The diagnosis of rupture of an aneurism of the mesenteric artery is nearly impossible, because of the difference in the symptoms which have been observed in particular cases, the absence of characteristic symptoms and the frequent presence of anomalous symptoms, and in the greater majority of cases the diagnosis has only been made at the autopsy.

Complete Atrophy of the Stomach.—Von Cakovic (*Archiv f. klin. Chir.*, 1902, Band lxv., Heft 2) recommends jejunostomy in the following types of cases: (1) In marked stenosis of the œsophagus, when gastrostomy cannot be performed because of the atrophy of the stomach. (2) In those cases of carcinoma of the stomach when a radical operation is either contraindicated or it cannot be performed. (3) In cases of stenosis of the pylorus or cicatrix of the stomach where the patient is very weak or the cicatrices are apt to be multiple. (4) In cases of ulcer of the stomach with frequent hemorrhages which do not respond to treatment and there is danger of death from inanition. (5) In all cases of poisoning by corrosive liquids where there is danger of death either from rupture of the stomach, or inanition, or as the result of such corrosion, when no other operative measure is possible. (6) In all cases of insufficiency of the sutures after operations upon the stomach when any other method of relief is impracticable. (7) When a radical or palliative operation has proved to be a failure. The results of jejunostomy are not very encouraging, and this is not surprising when one considers that this is an operation which has been reserved as a last resort, either when other operative measures have been tried and proved to be failures, as the disease is so extensive that no other operation is possible. The author reports sixty-seven cases, with twenty-five deaths due to the operation, or a mortality of 37.3 per cent.

The Diagnosis of Tuberculous Peritonitis in Children.—Kissil (*Archiv f. klin. Chir.*, 1902, Band lxv., Heft 2), after an interesting review of this subject, states in conclusion: (1) Tuberculous peritonitis is more common in children than is usually believed to be the case. (2) Many of the cases of so-called "spontaneous ascites" are in reality cases of ascites the result of a tuberculous peritonitis. (3) In many cases of tuberculous peritonitis the exudate will become absorbed under an appropriate tonic treatment, and eventually the patient will entirely regain his health. (4) In the majority of cases the onset of the disease is unnoticed. The first thing usually noted is that the child has become thin and pale without apparent reason. (5) The presence of a serous pleurisy at the same time as the tuberculous peritonitis markedly facilitates the diagnosis. (6) The most valuable diagnostic

symptoms are those caused by the presence of adhesions. (7) Examination of the fluid removed from a case of tuberculous peritonitis will show that it is rich in albumin and of high specific gravity. (8) Operation generally shows that the entire pericardium is involved in the tuberculous process. (9) The diagnosis is especially difficult in cases of chronic ascites complicated by tuberculous pericarditis. (10) It is very exceptional that the onset of tuberculous peritonitis is anything but insidious.

Carcinoma of the Lips.—JANOWSKY (*Archiv f. klin. Chir.*, 1902, Band lxv., Heft 2), as a result of an extensive review of the literature, states in conclusion: (1) The operation for carcinoma of the lips should not be considered as dangerous, and in the greater majority of cases union by first intention takes place in from nine to fifteen days. (2) All the lymphatic glands of the submental and submaxillary region must be removed, or recurrence will occur. (3) When necessary the inferior maxilla may be resected without danger. (4) The lymphatic glands are affected soon after the onset of the disease—in two or three months—but this should not prevent a radical operation from being successful. In many cases the glands are involved when not palpable, and recurrence will follow if they are not removed. (5) In 49 per cent. of the operated cases the end results were good. (6) In the cases which had recurrence the disease reappeared in the greater majority of cases within six months and nearly all the rest within the first year; in only a very few cases was the recurrence after a lapse of one or two years. (7) When recurrence took place it was generally found at the point where the disease first appeared or else in the submental region. (8) The operative results were influenced by the duration of the disease and the degree of malignancy in each particular case. Cases which were not severe were operated on successfully as late as several years after the onset of the disease. (9) Old age is not a contraindication to operation; the best operative results were obtained in patients between sixty and seventy years of age. (10) In cases of recurrence a second operation is only palliative and possibly may prolong life for several years. (11) Carcinoma of the upper lip is nineteen times less frequent than that of the lower lip, and carcinoma of the lip is ten times more frequent in males than females. In women carcinoma of the upper lip is five times more frequent than it is in men. (12) After a careful study of 178 cases, it is impossible to state that carcinoma of the lips is more frequent in any occupation or station in life than in any other. (13) The disease is most common in persons between the ages of sixty and seventy years. (14) Twenty-five per cent. of all the cases are rapid in growth and markedly malignant, 15 per cent. are less severe, while the remaining 60 per cent. are a compromise between these two.

What is the Prognosis in Tubercular Spondylitis?—MOSHER (*Brooklyn Medical Journal*, January, 1902) states that the consideration of the prognosis devolves the necessity of bearing in mind that tubercular spondylitis is nearly always a disease of childhood and that early diagnosis, with proper and rigid treatment, influences very strongly the ultimate results. The predisposing causes of Pott's disease are traumatism, hereditary syphilis, tuberculosis, anæmia, scrofulosis, scorbutus, and malnutrition from any cause. The exciting causes are fevers, sudden chillings of the body, overexertion of the

spine, and traumatism. There seems to exist among the profession as well as the laity the idea that traumatism is the only cause of tubercular spondylitis. The author believes that in the vast majority of cases, without the existence of a marked predisposing etiological condition, the slight injuries so often assigned as the cause of spondylitis would have no special significance. This disease begins insidiously with indefinite symptoms such as malaise, fever, night-cries, restlessness, lassitude, loss of appetite, indifference to surroundings, emaciation, irritability, and peevishness, all of which are more or less common in the severe illnesses of childhood. The pathognomonic sign is spinal rigidity, and it is the first marked symptom to attract attention, and is manifested by the child's attitude, which is characteristic. Later comes spinal deformity, progressing, abscesses opening, usually at some distance from the seat of the disease, and paralysis, more marked in the motor nerves, affecting the parts below the deformity. For a vast majority of cases it is possible to diagnose Pott's disease before there exists any apparent deformity. The diagnosis with the late symptoms present, such as deformity, abscesses or paralysis, is very easy, and is usually made by the parents, who will venture the information that the child has been ailing for some time and has been treated for various diseases. In the earlier stages, however, where the symptomatology is obscure, it becomes more difficult, but with proper attention to history, a thorough examination and careful arrangement of symptoms the number of self-diagnosed cases will be greatly reduced. This disease seems to lack to a marked degree the *vis medicatrix naturæ* existing in most diseases, and, therefore, instead of days and weeks, months and years are required for its cure, or even to stay its progress. To improve the patient's general health, to lessen and relieve pain, to prevent traumatism by, as far as practical, preventing the movements of the spine, to take the weight of upper part of body off the spine, to avoid, if possible, any deformity, or, if one already exists, to prevent its increase, are marked indications for the treatment of tubercular spondylitis. It is important that the patient's resistance be kept at the highest point by the judicious use of the proper medicinal agents indicated in each individual case. Iodoform (internally), creasote, syrup of the iodide of iron, cod-liver oil and stimulants have all proved of value in the author's experience. In the mechanical treatment recumbency seems to offer the best results in active spondylitis. By this is meant recumbency just so long as there is any tenderness or active disease.

Abscess and paralysis are the usual complications and indicate that the spine is not receiving proper support. Aspirations may be repeated in abscess, but where aspirations fail to obliterate the sac, or the pus is of such a character that aspiration is impossible, or when there is external inflammatory evidence, the abscess should be opened and drained, and, if psoas, counter-drained, vigorously swabbed out with gauze (not curetted), thoroughly irrigated, treated aseptically, and recumbency adopted. The paralysis due, supposedly, to inflammatory lesions more than pressure, should be treated by recumbency and counter-extension and by iodide of potash in increasing doses. This treatment usually takes many months, but if it fails Colot's forcible correction is in order. Laminectomy, owing to its seriousness, is not so encouraging. The author reports fifty-three cases of tubercular spondylitis, ranging in age from fifteen months to sixteen years, the average age being six years. In five

cases the cervical vertebræ were involved; in ten cases the cervicodorsal region was involved; in twenty-five cases the dorsal vertebræ were involved; in three cases the dorsolumbar region was involved, and in nine cases the lumbar vertebræ were involved. The time of treatment varied from one year to seven, average three and a half. Three cases were treated by recumbency alone; four cases were treated by brace alone; forty-six were treated by recumbency assisted by jackets, braces, etc. Time of recumbency one month to five years. Average two and a quarter years. Twelve cases suffered from abscesses, one from empyema, five from paralysis, one from hip-joint disease, and two from phthisis pulmonalis. Four cases had no deformity, twenty-five slight deformity, ten moderate deformity, and fourteen marked deformity when last seen. Seven died.

PEDIATRICS.

UNDER THE CHARGE OF

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Glandular Reaction in the Diseases of Children.—LABBÉ and BERTIN (*La Presse Médicale*, January 29, 1902, p. 99), in a thoughtful paper under this caption, point out that in the first years of life the lymphatic glands, like other lymphoid structures, have acquired their full anatomical development and are in their highest functional activity. They give origin to lymphocytes whose passage in great numbers into the circulation determines a leucocytosis distinct from that of the adult. In the course of divers acute and chronic affections they react with an intensity far beyond that manifested by the glands of the adult, the intensity of the reaction often being disproportionate to that of the excitation, so much so that the glandular reaction often appears to constitute the entire disease. This intensity of glandular reaction constitutes one of the peculiar characteristics of disease in childhood.

This peculiar physiological activity of the child's lymphatic system, which by its local functions arrests and destroys morbid germs, or at least attenuates their virulence, by producing leucocytosis, serves to explain why certain infections like pneumonia and typhoid fever are more benign in general in the child than in the adult.

The authors conclude by expressing the hope that artificial provocation of this activity of glandular reaction may be taken advantage of in the treatment of disease.

A Stigma of Degeneration Observed in Cretins and Idiots.—KOPLIK and LICHTENSTEIN (*Archives of Pediatrics*, February, 1902, p. 81) describe a hitherto unmarked anatomical sign observed in cretins and several types of

idiots. This is a prominence in the region of the antithenar eminence over the position of the pisiform bone. This prominence is immediately adjacent to the groove which separates the palm of the hand from the forearm. It is distinctly localized to this part of the antithenar eminence, and, viewed from the side, rises abruptly from the groove, giving a bayonet-like appearance. It is apparently an over-development or hypertrophy of the small muscles of the inner border of the hand attached to the os pisiformis, as well as, perhaps, an enlarged condition of the bone itself. Inasmuch as this prominence was observed in a cretin only three months old, it seems just to assume that it is a congenital anomaly and not a hypertrophy caused by the act of crawling on the hands and knees, as was first thought from its resemblance to a similar prominence seen on the forefoot of the domestic cat. This prominence has not been seen in a perfectly normal infant or child. It was observed in idiots, cretins, microcephalic idiots, and children congenitally deficient. So far it has not been seen in the Mongolian idiot, though a large number of cases of this affection have been examined. It has been found in all cases of cretinism, was absent in a case in which there were certain physical signs of cretinism, but in which the child was quite intelligent. It was also found in two markedly intelligent children with macroglossia and polydactylia.

The authors are not prepared to draw any definite conclusions, but consider this prominence a true anatomical stigma of degeneration, and, as far as cretinism is concerned, a highly interesting part of the symptomatology of this disease.

Syphilitic Enteritis under the Form of Melæna Neonatorum.—Esser (*Archiv f. Kinderheilkunde*, 1901, Bd. xxxii., S. 177) reports the observation of a newborn baby in which melæna appeared on the fifth day after birth, causing death six days later. The mother was a primipara of healthy appearance; the father was unknown.

At the autopsy the site of hemorrhage was found in the jejunum. Here there was a thickening of the mucosa due to a circular infiltration of small cells, with the formation of several ulcerations. This diffuse infiltration was particularly accentuated about the vessels, where in places it had produced obliteration. Analogous lesions were found in the liver and in the spleen, the latter being hardened and enlarged. There was also a certain degree of osteochondritis in the bones that were examined. This ensemble of lesions marked the melæna in this case as of syphilitic origin directly dependent, upon a specific ulcerative enteritis.

A Contraindication to Circumcision.—Rey (*Jahrbuch f. Kinderheilkunde* June, 1901) cautions against indiscriminate circumcision. He calls attention to the fact that in infancy there is what may be called a physiological phimosis, so that retraction cannot be made without exerting undue force. The preputial orifice expands during childhood, so that by eight years of age it can usually be retracted readily. Unless obvious symptoms are produced by an exaggeration of this physiological condition of the prepuce in infancy operation is unnecessary. The period of life up to the fifth year is one in which cystitis and urethritis are common complaints, and urinary troubles during this period are very rarely due to phimosis. The existence of urethral

or cystic disease is the strongest contraindication against producing a wound at the end of the penis.

In the presence of cystitis, which is first indicated by an ammoniacal odor of the napkins, the exposed skin surfaces become irritated and the prepuce becomes inflamed or ulcerated from evaporation of the urine and external pressure. If, however, there is no prepuce in front of the glans the urethral orifice is liable to ulceration, which may be followed by stricture, with its train of secondary sequelæ, or may leave scars that in later life may set up incontinence of urine of an intractable character.

The author, therefore, believes that the prepuce is really a great protection to the glans in the presence of a cystitis, and he advises the avoidance of circumcision until after the fifth year, unless it be required soon after birth for obstruction not amenable to cure by simple dilatation.

Treatment of Typhoid Myocarditis in Children. — CALAMET (*Traitement médicamenteux de la Myocardite typhoïdique*, Thèse de Paris, 1902) considers that the bath treatment of typhoid is not contraindicated by the appearance of myocardial changes if the possibility of syncope is guarded against by subcutaneous injection of sulphate of strychnine or sparteine, by the application of an ice-bag over the heart, or by the injection of saline solution (Guinon).

In regard to the medicinal treatment of myocarditis, he admits the value of digitalis in dose of 20 to 30 drops of the tincture. Under its use the pulse becomes slower and increases in force, fulness, and regularity, and vascular tension increases. Its cumulative effect, its power of provoking asystole, and its slowness of action are disadvantages. Caffeine does not have a cumulative action, and it acts rapidly in dose of 0.25 to 1 gramme a day, by hypodermic injection. It sometimes has the inconvenience of producing irritation and even delirium. In these cases it advantageously may be replaced by sparteine. One or two syringefuls of a solution containing 40 centigrammes of sulphate of sparteine to 10 grammes of distilled water may be used. Camphorated oil (1 to 10) or sulphate of strychnine (one-fourth of a milligramme, $\frac{1}{267}$ of a grain) may be employed; and ergotin, in virtue of its vasoconstrictor action, has been successfully used by Demange.

Syncope may be treated by the usual methods: lowering of the head, flagellations, frictions, tongue traction.

Erythema Scarlatiniforme and True Scarlatina in the Course of Diphtheria.—LOBLIGEOIS (*Des érythèmes scarlatiniformes et de la Scarlatine vraie au cours de la diphtérie*, Thèse de Paris, 1902) calls attention to the importance of examination of the blood and the urine in determining the diagnosis between a scarlatiniform erythema due to the use of antidiphtheritic serum and a true scarlatina occurring in the course of diphtheria treated by the serum. Such a differential diagnosis is sometimes almost impossible by the clinical features alone. In these cases an examination of the blood at the beginning of eruption offers the following distinguishing features: *a*. Polynucleosis is more marked in scarlatina than in the erythemas due to serum. *b*. Eosinophiles are more rare in scarlatina. *c*. In the scarlatiniform erythema abnormal forms are encountered which are absent in scarlatina. Examination of

the urine also furnishes valuable aid: the diazo-reaction, which is very frequent in scarlatina, is exceptional in diphtheria, and particularly in scarlatiniform erythema.

THERAPEUTICS.

UNDER THE CHARGE OF

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Adrenal Extract and Hæmatemesis.—DR. J. ADAM presents a new method in the use of this remedy. Fenwick recently called attention to the good effects which he had obtained in the treatment of hemorrhage from the stomach by the ingestion of capsules of adrenal extract. It is interesting to notice that another British physician called attention to the same fact in much the same manner, namely Grünbaum, early in 1900. These observers agree in stating, it is well to remember, that when administered by the mouth this drug may cause violent vomiting, which in its turn will aggravate the hemorrhage; the new method overcomes this. The instance is reported of a young girl with an intense hemorrhage from the stomach, who, after having taken several doses of a number of tablets of the pulverized extract of the adrenal capsules, continued to vomit more or less fresh blood. In the presence of this intolerance of the extract by the mucous membrane of the stomach he substituted the rectum as the avenue for giving the drug. After having washed out the bowel with twenty grains of calcium chloride he injected into the rectum, at first every two hours, then every four hours, ten grains of the pulverized adrenal extract suspended in water. The hæmatemesis ceased completely and promptly. This fact should be remembered, because it seems to prove that this extract acts as hæmostatic, not in bringing about coagulation of the blood, but in causing contraction of the vessels which are bleeding. The power of the mucous membrane of the rectum to absorb the drug was certainly increased to a considerable degree by the large quantity of blood which the patient had lost, and similarly the action of the drug was increased by the same cause. The author also uses this drug during the course of surgical operations on tampons impregnated with adrenal extract, with the purpose of clearing the operative field of blood, and thus of making it accessible to view. The drug may also be employed to increase and prolong the effect of anæsthesia, with the aid of ethyl chloride, in the operations of minor surgery and in removal of teeth. For this purpose it is necessary to apply a small dressing soaked in the extract upon the region where ethyl chloride is to be applied.—*La Semaine Médicale*, 1902, No. 4, p. 60.

Action of Tetramethylammonium Chloride on Circulation.—E. FORMANEK states that fairly large doses of tetramethylammonium chloride injected into dogs first increase the blood pressure, then lower it, and finally again increase it The pulse at the same time is retarded. The same changes were noted on division of both vagosympathetic nerves. Preliminary injections of atropine render the retardation of the pulse insignificant, and the high pulse waves disappear, and it may even happen that there will be an acceleration with low pulse waves. It may therefore be said that the retardation depends upon irritation of the peripheral vagus, and that the drug has an action analogous to muscarine. Destruction of the medulla and the spinal cord did not affect the changes in pressure, which appeared to be due to irritation of the peripheral vasoconstrictor nerves, especially in the splanchnic area. The subsequent fall of pressure is due to direct weakening of the heart or its ganglia. A comparison of the tetra- with the mono-, di-, and trimethylammonium chloride shows that with increased methylation the blood pressure is increased and the direct heart action diminished.—*Archives Internationales de Pharmacodynamie et de Therapie*, 1902, vol. ix., fasc. 4 and 6, p. 483.

Treatment of Cardiac Dilatation.—DR. I. BURNEY YEO describes the modern causes of cardiac dilatation, ascribing to athletics a very important rôle. Within general limits, of late years three manifest causes have been at work in giving rise to the prevailing tendency to cardiac dilatation; these are, he says, the influenza epidemic, the abuse of muscular exercise, and the excessive use of tobacco. With reference to the prophylaxis of this affection following influenza, prolonged periods of physical rest are very valuable. In those cases in which overexertion has led to cardiac strain, the avoidance of all kinds of muscular effort must be insisted upon; gentle exercise alone should be permitted. When the condition has been induced by overexcitement, emotional or mental, or by the addiction to unwise habits, these causes must be sought out and corrected. An open air life in the country or at the seaside, gentle exercise, and a nourishing but light diet are remedial measures of importance. Some cardiac tonic may be advisable, and the following prescriptions are offered by the author: Iron and ammonium citrate, 2; tincture of digitalis, 1; aromatic spirit of ammonia, 3; infusion of columbo, 24. Of this two tablespoonfuls twice a day, an hour after meals, are to be taken. He prefers, however, in the less serious forms, to employ strophanthus, or strychnine, or nux vomica, with coca, in combination with iron, quinine, or arsenic, as may seem desirable. The following has been serviceable: Quinine sulphate, 1; tincture of nux vomica, 4; fluid extract of coca, 4; spirit of chloroform, 5; water to 32. Of this two tablespoonfuls twice a day, an hour before food, are to be taken. In purely anæmic cases iron and nux vomica, together with some aperient to insure a regular action of the bowels, will be most appropriate, as: Dried iron sulphate, 1½; soap, ¾; powdered nux vomica, 1; aloin, ½ gr. as a pill. One or two (as necessary) twice a day, after lunch and dinner. In cases of somewhat acute dilatation, however induced, the hypodermic injection of strychnine in doses of $\frac{1}{60}$ to $\frac{1}{30}$ of a grain will often be attended with remarkably good results. In extreme cases of cardiac dilatation the ventricular muscle will often be found to be in a state of advanced degeneration, and digitalis

and other cardiac tonics will usually fail in producing any restorative or strengthening effect on it. Our chief resource in such a case must be the most absolute repose, with careful attention to the general nutrition. Light, easily digested, or predigested, highly nutritious food must be prescribed—such as pounded meat very little cooked, beaten-up eggs, chicken and game, a little whitefish when agreeable, milk, and a small quantity of good, sound wine, or a little weak brandy or whiskey and water, but the total amount of fluid taken must be strictly limited, so as not to augment the volume of blood. A regular action of the bowels must be maintained by suitable aperients. Free action of the bowels is very advantageous in nearly all cases of cardiac dilatation and feebleness. Aperients should, however, be so given as to clear away only the residue of digestion. For this purpose the best method is to give an aloetic pill after dinner or at bedtime and a saline dose early in the morning, about an hour before breakfast. Careful attention must, of course, be given to the individual sensitiveness to aperient medicines.—*Practitioner*, 1902, vol. lxviii. p. 281.

Dilatation of the Heart in Children.—Dr. Eustace Smith reports that cardiac dilatation, to a moderate extent, is far from uncommon in early life; indeed, in childhood the heart may be said to dilate with especial ease. The dilatation may be found out apart from any valvular affection; it is due to blood pressure in a flabby, ill-nourished or degenerated heart, and may occur without there being any resistance to the passage of blood from the heart. Acute infections, such as bronchopneumonia, diphtheria, and acute rheumatism are particularly liable to cause this. In any such case of acute disease where the dilatation is rapid, a recumbent position should be enforced, and on no pretence should the patient be allowed to lift even his head from the pillow. The diet should be regulated so that those foods that tend to ferment and fill the stomach with wind should be forbidden; baked apples, grapes, oranges, and acid fruits are to be avoided. The patient should be fed with milk, custards, strong soups, yolk of egg, and rusk. In the matter of drugs, if the case be a rheumatic one, and sodium salicylate being taken, it is well to combine with it five to ten grains of iron ammonio-citrate. Strychnine is of great value, and iron perchloride with solution of strychnine, given in full doses well diluted with aërated water, is held by the author to be very valuable. Alcohol should not be forgotten, and the author thinks well of the brandy-and-egg mixture of the *British Pharmacopœia*.—*Practitioner*, 1902, vol. lxviii. p. 56.

The Treatment of Gout.—Dr. A. P. Luff says that quite apart from the treatment of an attack of gout, which is a comparatively easy and simple affair, must be considered the treatment of the conditions which lead up to the attacks. Unstable metabolism is the keynote of this instability of the digestive, the nervous, and the circulatory systems, and the main point in treatment is to determine which set of organs is mainly at fault, and devote the major portion of the treatment to the remedying of such disturbance. He speaks specifically of several lines of treatment. Of the alkalies, the potassium salts of citric and carbonic acids are mostly employed. When combined with colchicum, excellent results seem to be assured. He prefers the combi-

nation of potassium citrate and colchicum. Sodium salts are not contraindicated, but are of less service unless they are used as cathartics. Lithium salts are even less useful than potassium or sodium. He maintains that lithium salts are more toxic than the others, and that the continued use of so-called lithia tablets is specious and wrong. If the gouty attack is combined with constipation and other indubitable signs of hepatic torpor, there is no better treatment at the outset than a dose of calomel or blue pill at night, with Epsom or Carlsbad salts in the morning. Subsequently a pill containing a small dose of calomel combined with euonymin and colocynth will be found most useful. A combination of sodium bicarbonate, gentian, and nux vomica taken a quarter of an hour before meals has proved very useful as a digestant in such cases. Baths, massage, galvanism, superheated, radiant heat are all advisable adjuncts to the drug treatment, but care must be exercised in the selection of the patient and the selection of the procedure as well. In the treatment of gouty eczema attention should be paid to two things: The bowels should be freely opened by blue pill or calomel and followed by a saline; and total abstention from alcohol in any form, red wines especially. As a local application lead subacetate, liquor carbonis detergens, one drachm of each to a pint of aqua sambuci, to be followed by a simple dusting-powder. Carbolic-acid lotions may be advisable to relieve pruritus. Sulphur baths are at times necessary. Dyspepsia should be avoided. Insomnia, which is a usual symptom, needs the free use of calomel. Moderate indulgence in tobacco is not contraindicated. From the side of prophylaxis of the attack, Luff believes in guaiacum resin, basing his hypothesis on the hepatic stimulating properties of this drug. He prescribes the powdered resin in cachets, five grains thrice after meals and gradually increasing the dose to ten or twelve grains. From a somewhat limited experience in the use of quinic acid, he is inclined to believe in its efficiency. The dietary of a gouty patient cannot be laid down in hard-and-fast lines; it is largely an individual question. Simplicity is desirable, and the consumption of large amounts of water are advised both at meals and between periods of eating. As far as climate is concerned, a fairly bracing air, with low, relative humidity is most suitable. High mountain air and low, wet valleys are not advisable resting places. Exposure to east and northeast winds is to be avoided, and residences by the sea are not to be chosen.—*Practitioner*, 1902, vol. lxviii. p. 297.

Blood and Urine in Syphilis.—Dr. E. Buffa, in his conclusions on the condition of the urine and blood in syphilis, says that (1) the urine of syphilitics, far from being hyperacid, is, on the contrary, hypoacid, and that this hypoacidity is but little diminished by a stay in the hospital; (2) the acidity of the blood also suffers a considerable diminution; (3) the mercurial cure, acting upon the body in general, and probably the liver in particular, increases the hypoacidity of the urine, and consequently also the blood; (4) finally, the mercurial cure, specifically for the syphilitic manifestations, is insufficient to bring on a complete cure, and it is necessary to combine with it a treatment acting upon nutrition in general and upon the nervous and hepatic functions in special—*Archives Internationales de Pharmacodynamie et de Therapie*, 1902, vol. ix., fasc. 5 and 6, p. 495.

GYNECOLOGY.

UNDER THE CHARGE OF

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ASSISTED BY

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Dysmenorrhœa.—THEILHABER (*Centralblatt für Gynäkologie*, 1902, No. 3) calls attention to the fact that a thorough revision of our views on this subject has become necessary in the light of recent experience. In his opinion more than 75 per cent. of the cases of painful menstruation are not dependent upon anatomical causes. The pain is really due to tetanic contraction of the circular muscle at the os internum, such as occurs in other sphincter muscles in neurotic subjects. He opposes Menge's theory that dysmenorrhœa is due simply to an exaggeration of the contractions of the longitudinal muscular fibres, which always accompany normal menstruation. If, he argues, the symptom is due purely to mechanical obstruction it should invariably disappear after childbirth, which is not the case in nervous and hysterical women. Uterine colic cannot be due only to the passage of clots, since in many typical cases of dysmenorrhœa there is a free escape of fluid blood. Moreover, the pains are often most severe from twelve to twenty-four hours before the flow appears, instead of on the second or third day, when it is most profuse and clots usually appear.

Apparent Abdominal Tumors.—EINHORN (*Berliner klin. Wochenschrift*, 1901, No. 43) found enlargements of the abdomen in 42 out of 6045 patients examined by him, which were not due to neoplasms. These were situated in the epigastric or hypochondriac regions, and are included by the writer under four classes—viz.: Prolapse of the left lobe of the liver, thickening and prominence of the abdominal aorta, localized hypertrophy of the muscles of the parietes, and probable adhesions around the lesser curvature of the stomach.

These are distinguished from true neoplasms by their smooth surface and more sharply defined outline. The site of the enlargement gives some clew as to its possible character. There is normally marked enteroptosis in the conditions before mentioned, while the history of each case shows that it is of long standing.

Uterine Castration.—PINCUS (*Centralblatt für Gynäkologie*, 1902, No. 8) under this term refers to the abolition of the functions of the uterus by means of atmocausis. He reports cases of women with phthisis and Bright's disease in whom obliteration of the uterine cavity by the introduction of steam not only eliminated the metrorrhagia, which threatened to shorten the life of the patient, but prevented future conception—a most undesirable event

under the circumstances. The writer concludes that the operation is only justifiable in the case of women with incurable diseases.

Radical Operations for Cancer of the Uterus.—WERTHEIM (*Centralblatt für Gynäkologie*, 1902, No. 8) reports 77 cases of abdominal extirpation of the cancerous uterus, glands, and broad ligaments. Of the last 27 operations only one terminated fatally—from pulmonary embolus on the fifth day—which fact would seem to show that the immediate results are not so bad as they have been represented. By clamping the vagina below the cervix previous to removing the uterus sepsis can be certainly avoided.

Necrosis of the wall of the ureter occurred only once in the last 17 cases, due to greater care in preserving the vascular supply of the duct. Cystitis is a common complication after the operation. The writer is not yet willing to give his conclusions with regard to the ultimate value of the radical operation, although his oldest cases have been under observation for three years.

With regard to the indications for removing the glands, the writer states that he does not disturb them unless they are distinctly enlarged, since careful microscopical studies have shown that cancerous foci are not present otherwise. He admits, however, that experience may prove that this rule is not always a safe one.

Treatment of Inoperable Cancer of the Uterus.—TORGGIER (*Münchener med. Wochenschrift*, 1901, No. 30) has abandoned the use of dry powders, preferring peroxide of hydrogen. He reports 260 cases of inoperable cancer treated by tamponade of the vagina with iodoform gauze saturated in pure peroxide, which is left *in situ* for three or four days. After removal of the gauze as much of the diseased tissue as possible is removed with the sharp spoon, the raw surface is cauterized, and is then covered for a few minutes with cotton soaked in 40 per cent. solution of formaldehyde. Within from six to ten days a slough is thrown off, leaving a dry wound.

Vaginal Puncture and Incision.— FRANZ (*Münchener med. Wochenschrift*, 1901, No. 31) reports 81 cases of diagnostic puncture through the posterior vaginal fornix. This is especially valuable in cases in which it is impossible to make a positive diagnosis between retro-uterine hæmatocele and abscess of the tube or ovary.

The writer seems to be opposed to explorative vaginal incision, especially in cases of hæmatocele. He lays stress upon the importance of using a large, long needle and observing strict asepsis.

Antero-lateral Colpotomy.—DÜHRSSEN (*Berliner klin. Wochenschrift*, 1901, No. 44) describes under this heading a new method of colpo-cœliotomy, the advantages of which are as follows: 1. The broad ligaments being first divided, before the peritoneal cavity is opened, it is possible to evacuate abscesses extraperitoneally. 2. The subsequent extirpation of the adnexa is easier. 3. The uterus can be drawn down to the vulva, rendering the tubes and ovaries more accessible. 4. Infected stumps can be brought down and sutured to the side of the vagina. 5. Drainage is more perfect than when the gauze is introduced through a posterior incision. 6. The antero-

lateral method permits more perfect hæmostasis, and thus renders total extirpation unnecessary. Partial incision of the broad ligament is recommended in the case of a large ovarian or tubal abscess situated laterally. Complete separation of the ligament is preferable in the presence of extensive exudates with fixation of the uterus, with infected stumps, and when thorough drainage is indicated. Bleeding from the posterior surface of the uterus after the separation of adhesions, or from deep tears, is best reached and controlled in this way.

Prolapse of the Urethra.—GLAEVECKE (*Münchener med. Wochenschrift*, 1901, No. 22) states that only 150 cases have been reported, to which he adds another. The principal cause of this condition is relaxation of the tissues in consequence of the poor general condition of the patient, senile involution, or frequent child-bearing. Circular incision of the prolapsed portion and suture of the wound is the only proper method of treatment. [We do not understand why the writer should regard this condition as so rare, having operated upon two well-marked cases in old women within the past fortnight.—ED.]

Parametritis Posterior.—MUELLER (*Centralblatt für Gynäkologie*, 1902, No. 9) concludes an article on this subject with the statement that the condition usually described as retroposition of the uterus, or pathological anteflexion, resulting from inflammatory shortening of the sacro-uterine ligaments, is really due to inflammation of the rectum at the point where it is surrounded by these ligaments. He believes that the cases are rare in which parametritis posterior is secondary to uterine infection.

The treatment, therefore, should be addressed to the intestinal trouble, being practically the same as that of colitis. He uses injections of tannin, oak-bark, permanganate of potash, protargol, nitrate of silver, etc., with careful regulation of diet and laxatives. Vaginal massage is recommended to stretch the shortened ligaments, or rather perirectal exudates. The best results are obtained by making simultaneous pressure through the rectum by means of a thick sound or bougie. Electricity is also recommended.

Traumatic Granuloma of the Bladder.—KOLISCHER (*Centralblatt für Gynäkologie*, 1902, No. 10) reports four cases that were clearly due to prolonged trauma in a bladder which was the seat of inflammation. The symptoms were tenesmus and a feeling of fulness in the bladder. Hemorrhages were frequent and copious, and the urine was loaded with phosphates. Through the cystoscope one or more bright-red sessile growths were seen, always at the site of a cicatrix. These were quite vascular, and bled at the slightest touch, although they were not sensitive. The usual applications employed in cystitis do no affect granulomata, which must be excised, preferably through the cystoscope. Bleeding is usually sharp, but may be controlled by suprarenal extract. Recurrence does not occur after complete removal.

OBSTETRICS.

UNDER THE CHARGE OF

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Attempted Criminal Abortion in Ectopic Gestation.—In the *Boston Medical and Surgical Journal*, January 9, 1902, SWAN reports the case of a patient about seven weeks pregnant, who had instruments introduced within the womb to produce abortion. On the ninth day afterward she was attended by two physicians who examined and curetted the uterus. The patient died in the afternoon of the following day. Upon autopsy the peritoneal cavity contained three pints of dark fluid and clotted blood. In the right Fallopian tube was a ruptured swelling, from which protruded clotted blood and fine filaments. The right ovary contained a corpus luteum. The patient evidently perished from ruptured ectopic gestation.

The direct evidence of criminal abortion had been removed by dilatation and curetting; accordingly, the only assignable cause for death was ruptured ectopic gestation, and the abortionist escaped prosecution.

[This case is an illustration of the many circumstances which protect the criminal abortionist. A physician's first impulse when summoned to a case of pelvic septic infection following criminal abortion is to cleanse the uterus by curetting. By so doing, however, he destroys the evidence of the abortion, and the abortionist usually escapes prosecution. It is better in such cases, before interfering in any manner, to notify the authorities and to give them an opportunity to secure evidence. Then dilatation and curetting, if necessary, may be performed. A further reason for delay lies in the fact that many of these patients, after criminal abortion, suffer from exhaustion, through hemorrhage and infection. They are ill-prepared to endure an anæsthetic and an operation. A better result is usually obtained if sufficient delay is practised to build them up by stimulation.]

The Treatment of Placenta Prævia.—In the *Boston Medical and Surgical Journal*, January 2, 1902, HIGGINS reported the results of seventy-five cases of placenta prævia, of which fifty-six were treated in hospital wards and nineteen in out-patient service in their homes. Among the house cases there were six deaths, a mortality of 10.7 per cent. Of these six, five were complete placenta prævia. Of the nineteen out-patients there were two deaths, one of the complete and one of the incomplete variety of placenta prævia, a mortality of 10.5 per cent. Of the seventy-five cases there were eight deaths, a mortality of 10.6 per cent. These cases were treated by the use of the tampon and occasionally by the employment of forceps. Sixty-two per cent. of the children were born prematurely.

The method of treatment described and most usually employed consisted in the induction of labor so soon as the diagnosis is made by rupturing the membranes and packing the vagina tightly with dry sterile gauze. Under the influence of the gauze-packing hemorrhage is controlled and dilatation proceeds and, if necessary, the patient can be finally delivered by forceps or version.

The purpose of this paper is to criticise the performance of Cæsarean section for placenta prævia. The writer quotes the results of thirty-two Cæsarean operations in the Boston Lying-in Hospital during the last five years, with three maternal and three fœtal deaths, a mortality of 9.3 per cent. He believes that the general mortality of the Cæsarean operation is about 10 per cent. He gives three quotations from American writers, but makes no reference to the foreign literature of the subject. He draws attention to three cases of placenta prævia recently operated upon in the vicinity of Boston, with a mortality of 66.6 per cent.

In discussion Worcester would not condemn Cæsarean section for placenta prævia. He drew attention to the fact that aseptic precautions are more easily exercised in abdominal section than in prolonged labor with repeated vaginal packing. In placenta prævia the cervix is easily lacerated, and while he was satisfied with the ordinary methods of treatment in cases where the placenta is not central, in central placenta prævia he believed that there existed a field for the modern Cæsarean operation.

Donoghue has performed Cæsarean section twice for placenta prævia, with the recovery of one mother and two children. He believed that when the placenta is central Cæsarean section is indicated. It is also indicated in incomplete placenta prævia when malpositions are present and in cases where the mother has been delivered previously by operations. Others spoke in favor of Cæsarean section in cases where the os and cervix are tightly closed, the placenta central, the patient in good condition and in the hands of an operator competent to perform abdominal section.

During the discussion of this paper attention was called to the fact that obstetric cases are usually in the hands of those incapable of performing abdominal section. While this may be true in many cases, it is not in all, and is a condition which should not be so. No one is competent to attend obstetric cases who cannot deal with ruptured ectopic gestation by abdominal section or labor in contracted pelves, or who cannot operate in any manner to save the life of mother and child.

A Complicated and Fatal Case of Early Pregnancy.—In the *Centralblatt für Gynäkologie*, No. 1, 1902, HAEBERLIN reports the case of a patient, aged thirty-nine years, who had borne seven children and had been for the last year out of health. She complained of pain in the lower portion of the abdomen and marked distress in the stomach. She had failure of appetite, and the filling of the stomach caused intense distress. When seen she was eight weeks advanced in pregnancy and was growing much worse. She could not sleep, was ejecting all food and in a highly melancholy frame of mind. She was very anæmic, the skin dry and yellow, the tongue also dry. The action of the heart was regular, the pulse 80, small and with little tension, and the uterus was of the size commonly seen at eight weeks' gestation.

Because of the patient's threatening general condition it was determined to empty the uterus, and at the request of the patient and her husband to make further pregnancy impossible. Accordingly, the uterus was curetted, cleansed and packed with iodoform gauze. Abdominal section was performed and the Fallopian tubes were excised. There was some oozing of blood when the left tube was removed. In general the operation proceeded well and the patient roused quickly from the anæsthetic. Iodoform gauze was removed from the uterus on the following morning. The patient's pulse became very rapid and irregular. She had great apprehension, and complained of strong and tumultuous beating of the heart. The bowels acted after injections, the wound in the abdomen healed by first intention, and the patient gradually grew better. Five days after the patient had become convalescent she had a similar attack of rapid heart action and general distress, from which she gradually recovered.

The author suggests no definite explanation for this case. The character of the pulse resembled that of iodoform poisoning. Ileus might produce such symptoms also.

Cæsarean Section by Incision of the Fundus.—In the *Centralblatt für Gynäkologie*, 1902, No. 5, JUROWSKI reports the case of a patient, aged thirty-nine years, who lost her first child after tedious labor, and in whom the second and third labors were terminated by craniotomy. In her fourth labor the amniotic liquid was early discharged, and the patient brought to the hospital in labor. Upon examination the pelvis was considerably contracted, the internal conjugate being 7½ cm. The head was presenting, but not engaged. Cæsarean section was chosen and accepted by the patient, and the uterus opened by transverse incision across the fundus. The child was extracted by the feet, and the placenta easily removed. The bleeding was very slight, and ceased completely upon removal of the placenta. This was situated on the anterior wall of the uterus, its margin coming to the edge of the fundal incision. The patient made an uninterrupted recovery. Upon examination it was found that the uterus was adherent to the abdominal wall at the lower end of the abdominal incision.

The second case was a patient who had had hip-joint disease in childhood. She had been four times pregnant, and in the first labor had craniotomy, and in the second and third the child was lost in version and extraction. The external conjugate was 17 cm. The internal conjugate could not be measured because of the high position of the promontory of the sacrum. The head was high above the pelvic brim and the membranes had not yet ruptured. Cæsarean section by transverse incision was chosen, and at the operation the placenta presented and was rapidly torn through and delivered to avoid hemorrhage. The child was delivered by the feet, and the uterus closed in the usual manner. An excellent recovery followed.

The third case was a patient who had lost three children, one in spontaneous birth and two with the use of forceps. She had a contracted pelvis, with an external conjugate of 17½ cm. The head had not engaged, and the membranes were unruptured. The operation proceeded smoothly, and the patient made an uninterrupted recovery.

PATHOLOGY AND BACTERIOLOGY.

UNDER THE CHARGE OF
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Report of the Men Working under the Cancer Commission of Harvard University for the Year 1901–1902.—(*Journal of Medical Research*, 1902). It is claimed by the men who believe that cancer is due to parasites: 1. That a proliferation of the epithelial cells analogous to cancer can be produced by certain protozoa (nodules due to coccidium oviforme). 2. That certain skin lesions characterized by epithelial-cell proliferation are due to the action of a so-called protozoan, molluscum contagiosum. 3. That blastomycetes constantly are present in human cancers, and are the cause of the lesion. 4. That by experimental inoculations of animals with blastomycetes, true epithelial or cancerous nodules can be produced. 5. Finally, that the well-known endocellular bodies seen in the protoplasm of cancer cells have a definite morphology, are parasites, and cause cancer. It was the object of investigators whose work is here reported to study each of these questions.

Coccidium Infection of the Rabbit's Liver. Tyzzer describes the lesions produced by coccidium oviforme in the liver of rabbits. He finds that the lesions consist of small white or yellow nodules which always are connected with the bile-ducts and may occur as cyst-like or dense and firm structures. Histologically the nodules are composed of cysts into which project papillæ covered with epithelium, or there may be very little lining epithelium to the cysts, with a dense fibrous capsule and remote cirrhosis of the liver. The infection takes place through the stomach by the ingestion of a capsulated form, the oöcyst, in which develop eight actively moving sporozoites. The capsule is dissolved by the digestive juices, and the sporozoites are set free and invade the biliary epithelium. In the epithelial cell the sporozoite develops into a schizont, which divides and breaks up into falciform bodies, the merozoites, which in turn are set free and invade the biliary epithelium. This is the process of autoinfection.

There is also a process of sexual reproduction. Some of the organisms become microgametocytes, from which small male elements, microgametes, are developed, which fertilize the female form. Other forms may develop into macrogametes, the adult female form, which, becoming fertilized, develops a resistant envelope, the sporocyst; this adult organism set free passes out through the intestinal tract, and may infect other animals if ingested.

The histological changes are as follows: After invasion of the epithelium by the protozoan the epithelial cell degenerates and is destroyed. This produces a defect in the epithelial lining of the duct, and inflammatory exudation appears. Following the destruction of the epithelium there comes an increase in the underlying connective tissue which pushes into the bile-duct to form papillæ, and a proliferation of epithelium occurs in order to cover in the defect. Repair is brought about by walling off of the lesion by connec-

tive tissue. No metastases occur. In only one stage does the parasite in the least resemble the so-called "parasite" of cancer. The lesions produced by coccidium oviforme are essentially those of chronic inflammation.

MOLLUSCUM CONTAGIOSUM. WHITE gives a most complete and admirable review of the literature. The histological changes are described with accurate detail. The nodule is due to a hyperplasia of the rete cells, which push down and out and produce a globular tumor. The deeper layers consist of quasi-normal spinous cells with well-marked nucleoli, usually single or double, which stain deeply. Among these are cells with no nucleus and with fibrillar protoplasm. Nearer the surface are cells with distorted nuclei surrounded by a clear halo, or the cells may lose their nuclei altogether. In still more superficial layers the cells increase in size, the nucleus is pushed to one side, and the cytoplasm becomes honey-combed. Mitotic figures are common. In still higher layers the nuclei disappear and the cell looks like a multilocular cyst. Still higher, probably in the stratum granulosum, the cells become smaller, the trabeculæ disappear, and the cells become homogeneous with keratin-like walls. There are no bodies which resemble the gregarines, nor any doubly-contoured bodies. Often there is well-marked inflammation about the nodule. The staining reaction shows that the end result of the cell changes is the production of keratin—*i. e.*, the entire process is a peculiar metamorphosis of the rete cells into keratin.

The bacteriological work was done by ROBEY. He used ordinary bacteriological media and a special medium, a bouillon made of finely chopped human skin. Extensive cultural experiments showed the presence of no organism except the staphylococcus epidermidis albus of Welch. Inoculation of animals with this organism produced the usual staphylococcus inflammation; in others it produced no results. There was no other cultivatable parasite.

CULTURAL EXPERIMENTS OF MALIGNANT TUMORS. RICHARDSON made an extensive series of cultural experiments with fresh cancerous material obtained from operations at the Massachusetts General Hospital. He used a great number of different media. The cultures were observed over periods of time varying from fifteen days to months. The result of his investigations confirms his report of previous work, and he concludes that it is impossible to cultivate from new-growths anything which can be regarded as a specific infective agent.

FOUR PATHOGENIC TORULÆ. WEISS studied the morphology and cultural peculiarities of four blastomycetes (really torulæ), two of which have been isolated from cancer—one by Plimmer and one by Sanfelice. One came from fruit, and was said to produce cancer by experimental inoculation (Sanfelice's neoformans). One came from milk, and was pathogenic for rabbits (Klein). Weiss gives a systematic classification of the fungi, and says that the torulæ are micro-organisms similar to the saccharomycetes, except that they do not produce spores or develop mould-like vegetations (mycelia). As a rule, they have no power to produce fermentation, although a few can. Morphologically the torulæ cells are round masses of protoplasm, each contained in an envelope. It is doubtful if they have a nucleus. The protoplasm consists of a fine network of vacuoles and oil-drops. Sometimes in the vacuoles is a nucleus with Brownian movement. The membrane con-

sists of two layers, which sometimes can produce a gelatinous substance outside of the capsule, the nature of which is not evident. Weiss used special technical methods, as taught by the Copenhagen school. He found that the four organisms he examined did not ferment sugar, or form spores, or produce mycelia. He found after a certain length of a life of cultivation that each organism had constant morphological and cultural peculiarities which allow them to be differentiated. He considers all four organisms studied to be torulæ, and gives an extensive table of their characteristics.

Cell Inclusions in Cancer and in Non-cancerous Tissue. Greenough examined various tissues to see if bodies similar to the well-known cancer bodies exist in tissues other than cancer. He took as his standard of cell inclusion the form described by Plimmer in the *Practitioner* of April, 1899. He examined a large number of different tissues with entirely negative results. He examined also thirty non-malignant tumors of the breast, including acute and subacute mastitis, adenoma, adenofibroma, and myxofibroma. In eleven cases of chronic mastitis, which were non-malignant—that is, breasts which had round-celled infiltration with an increase of connective tissue, atrophy of the gland tubules, and cyst formation—there was no penetration of the epithelium beneath the basement membrane, and no marked increase of mitotic figures; in each of these cases he found typical inclusions like those seen in cancer cells. The nucleus of the cell in which these inclusions occurred was always near the basement membrane, while the inclusions were on the side nearest the lumen. Exactly similar conditions were found in eight adenofibromata of the breast, in one myxofibroma, in three out of four adenomata, and in eight cancers. In the cancers the inclusions, as a rule, were larger than in the other tumors of the breast. Greenough believes that since the inclusions are seen entirely in alveolar glandular carcinomata and in no epitheliomata they have to do with the process of secretion, and that they do not arise from nuclear degeneration.

From a review of the literature it is evident that in secretion in glandular epithelium there is associated a definite differentiation of the cell protoplasm, with which a protoplasmic body, the centrosome, is involved. Moreover, the great variation in size of the inclusions in cancer suggests secretion and accumulation, which may attain great size if the gland duct is occluded, as happens in cancers where the epithelial cells are massed together and no lumen is left. The inclusions occur more frequently in slowly than in rapidly growing cancers. The cells have probably lost their power of secretion with greatly increased capacity for growth. Inclusions in mitosing cells are very uncommon. He concludes (1) that cell inclusions of a constant type occur in practically all cases of cancer of the mammary gland; (2) that they also occur in non-cancerous disease of the breast, but (3) not in epitheliomata or sarcomata; (4) that apparently the staining reaction and situation of these bodies justify the hypothesis that they are the results of secretory activity; (5) there is no reason for believing that they are of parasitic origin.

The Relation of Blastomycetes (Torulæ) to Cancer. Nichols reviews the literature at some length. The idea that cancer is due to a blastomyces practically dates from a case reported by Busse, clinically considered to be a "soft sarcoma" or "chronic inflammation." Blastomycetes were present in the primary tumor and in internal metastases. They could

be cultivated in pure culture, and in animals produced local and secondary granulomata.

Sanfelice considered that the well-known cancer bodies were identical morphologically with blastomycetes. He cultivated in fruit juices a blastomyces which he obtained "from the air" the "saccharomyces neoformans," inoculated many animals, and produced local "tumors" with large lymph nodes and internal metastases. In but three cases did he claim to produce cancer, and in these cases there are no epithelial metastases, nor could he obtain his organism from the nodules.

Plimmer obtained a similar organism which he considered to be the cause of cancer, but by inoculation produced only "endotheliomata," not "cancer." Other men claimed that morphologically the cancer bodies were analogous to blastomycetes, but the evidence of this identity was very weak.

Many men inoculated animals with blastomycetes from animal or human tumors. They produced local and secondary lesions of inflammatory or granulation tissue, but never cancer, except Leopold, whose experiments were puerile. In human beings lesions, clinically sarcomata, but histologically granulomata, due to the action of blastomycetes, have been observed. A few cases of dermatitis, due to blastomycetes, have also been seen in human beings, but the lesion is essentially an intraepithelial inflammation, and is not analogous to cancer. In horses a disease clinically like glanders, due to the action of blastomycetes, has been observed.

Many men working with blastomycetes obtained in various ways have found many inert and some pathogenic; the pathogenic varieties produced only abscesses or nodules of granulation tissue. Some men working with Sanfelice's neoformans also produced granulation tissue in animals, but never cancer.

Moreover, yeasts are seldom found in cancers, and when present are found in ulcerating nodules and represent a secondary infection. The cancer bodies are not identical morphologically with blastomycetes; they are found in other lesions than cancer; they are not constantly present in cancers; when they are present they are not so situated, and do not occur in such numbers that they can be considered as the cause of the disease. The mere presence of blastomycetes in cancer, even if constant, is no proof that they are the cause of the disease.

Nichols inoculated thirty animals—eighteen with Sanfelice's neoformans, twelve with Plimmer's organism. There was always a local reaction, fever and abscess, or nodules of peculiar granulation tissue composed of connective tissue, many endothelioid cells, and relatively few bloodvessels. The blastomycetes were free or in phagocytic cells, and were always surrounded by a gelatinous capsule. Usually there was little acute inflammatory exudate, but there always were some plasma, lymphoid, and eosinophilic cells. In glandular organs the reaction was confined entirely to the interglandular connective tissue. There was no glandular proliferation. In the epidermis the epithelial cells were destroyed by contact with the blastomycetes. There never was proliferation. The lymph nodes always were enlarged, and were myxomatous or necrotic. Blastomycetes were free in the sinuses or were contained in the endothelial cells. Ultimately they destroyed the lymphoid tissue, which was replaced by a proliferation of connective tissue and endothelioid cells. In

the lungs the blastomycetes were in the alveolar wall, and caused a proliferation of connective tissue, which encroached upon and finally obliterated the alveoli. Often there were pneumonia and atelectasis. The liver practically always was free. In the spleen the follicles were primarily affected and were replaced by connective tissue and endothelioid cells. In the kidney the lesions were always in the cortex, beginning usually in the glomeruli, were composed of connective tissue and endothelioid cells, and destroyed adjacent tubules by pressure. The morphology of the blastomycetes was constant and not the same as that of cancer bodies.

Nichols' conclusions are the following: 1. Certain blastomycetes are pathogenic. 2. They produce in animals spontaneously infected acute inflammations, abscesses, or nodules of granulation tissue. 3. In human beings spontaneously infected they produce acute inflammation or proliferation of endothelium and connective tissue. The occasional proliferation of the epidermis is secondary to the chronic inflammation of the corium, and is not analogous to cancer. 4. Blastomycosis in human tissue is rare. 5. The lesions produced in animals experimentally are inflammation or nodules of granulation tissue. Sanfelice's "successful" cases are coincidents and not results. 6. The toxic power of blastomycetes is small. 7. Blastomycetes primarily extend along lymphatic clefts. 8. Rarely there may be a blood dissemination and general infection. 9. Secondary nodules are the same as the primary—*i. e*, composed of granulation tissue. 10. The morphology of the cancer body is not identical with the blastomycetes. 11. Blastomycetes are not constantly present in human cancers. 12. When they do occur they are not present in such numbers and in such a relation to the lesions as to justify the belief that they are the cause.

All of which leads to the ultimate conclusion that blastomycetes have nothing to do with the production of cancer.

General Conclusions. As a result of the work just reported it is concluded that: 1. The lesion produced by coccidium oviforme is essentially a chronic inflammation not analogous to cancer. 2. The lesions in molluscum contagiosum show certain changes in the epidermis not due to the action of protozoa and not analogous to cancer. 3. The so-called "blastomycetes" of Sanfelice and Plimmer are torulæ. 4. The lesions produced by these torulæ are essentially nodules of peculiar granulation tissue, not cancerous or in any sense "tumors." 5. Blastomycetes are not constantly present in human cancers. 6. The cancer bodies are not parasites or the cause of the lesions, but are probably atypical stages of the process of secretion by glandular epithelium.

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INDEX.

ABDOMEN, pigmentation of, 919
Abdominal operations, present method of treating ureters severed during, 676
section, drainage after, 363
tumors, apparent, 1104
wound, infection of, during operation, 920
Abortion and premature labor, treatment of, 550
Abscess, pulmonary, 347
Acetanilid-iodized starch powder as a local remedy, 936
Acid intoxication of diabetes in its relation to prognosis, 533
Actual cautery in treatment of corneal ulcers, 1074
Adenoid vegetations, treatment of, 720
Adrenal extract and hæmatemesis, 1100
Adrenalin chloride, therapeutic value of, 541
Affections of the mouth and throat, 187
Albumin, Bence Jones, observations on the nature of, 939
Albuminous expectoration following thoracocentesis, 620
Albuminuria after cold baths, 535
Alcohol, influence of, upon the natural resistance against infection, 704
in treatment of inflammation of pelvic organs, 181
Alcoholic multiple neuritis, report of a case of, 811
neuritis, 735
Alkalinity of the blood in physiological and pathological conditions, 165
Alopecia areata, contagiousness of, 558
Anæsthesia, spinal, 715
Analgesic antipyretics, 721
Anatomy of round ligament, 360
Anders, J. M., the association of pulmonary tuberculosis with both primary and secondary endocarditis, and the effect of valvular disease upon lung tuberculosis, 93
Andrade, E., case of ophthalmia neonatorum caused by the diplobacillus of Morax and Axenfeld, 284
Aneurism of mesenteric arteries, 1093
Aneurisms of the thoracic aorta, cause of death in, 72
Angina pectoris, 225
Angioneuroses of skin, 935
Ankylostomiasis, 28
Antero-lateral colpotomy, 1105
Antidotes for cyanide poisoning, 178
Antityphoid inoculation in the case of an epidemic of typhoid fever in the Richmond Asylum, Dublin, 345
Anzinger, F. P., changes occurring in striped muscle in the neighborhood of malignant tumors, 268
Aortic insufficiency, case of, 1022
Apparent contagion in rheumatism due to Meyer's diplococcus, 1090
Appendicitis in connection with pelvic disease, 546
practical observations on, 912
Aristol in hay fever, 724
Arnold, H. D., cause of death in aneurisms of the thoracic aorta which do not rupture, 72
Arnold, J., recent cell studies of, 748
Arsenic, action of, on healthy tissues of the skin, 175, 176
and beriberi, 917
medication by latent, 175
Articular rheumatism, acute, 716
Artificial serum, use of, as a means of prognosis in diphtheria, 720
Arytenoid cartilage, dislocation of, 745
Ascaris lumbricoides, 905
Atlee, L. W., case of alcoholic multiple neuritis, 811
Atony of uterus causing external hemorrhage during gestation, 737
Atresia, genital, 919
Atrophy of stomach, 1094
Auto-intoxication for intestinal obstruction, 539

BABINSKI'S toe phenomenon, 164
Bacillus of Eberth, presence of, in the blood and in the rose-spots during typhoid fever, 903
typhosus, 595
Bacteria, influence of ozone on, 185
pigment, effects of change of color upon, 647
Bacterial contamination of milk, 937
Bacteriology of gall-bladder, 372
Bacteriolysis and typhoid immunity, 706
Balantidium coli, pathogenic importance of, 906
Baldness, crude petroleum of no value in, 934
Baths, cold, 535
Beard and hair of scalp, complete loss of, followed by improved vision, 556
Beck, C, corrected mal-union in fractures of the radius and ulna of both forearms, 616
Bettmann, M., report of a case of fibrinous bronchitis, 304
Bile acids, intermediary circulation of, 150
-ducts, cancer of, 343
retention, influence of, on the secretory activity of the stomach, 704
Bladder, rupture of, 539
traumatic granuloma of, 1106
Blastomycetes, relation of, to cancer, 1112
Blindness from congenital deformity of the occiput, 4
Blood and urine in syphilis, 1103
examinations, diagnostic value of, in gastric ulcer and carcinoma, 342
in tuberculosis, 703
Blue pigmentation following injections of morphine, 559
Boric acid and borax, influence of, upon the general metabolism of children, 561
Boyd, G. M., hypernephroma of kidney complicating pregnancy, 1069
Brain abscess in typhoid fever due to bacillus typhosus, 595
disease, Kernig's sign as a symptom of focal, 772
Briggs, C. E., laparotomy for perforation in typhoid fever, 38
Bronchitis, fibrinous, 304
Burnett, C H., scarlatinous empyema of the anterior superior squamomastoid cells, 394
Buxton, B. H., paratyphoid infections, 976

CÆSAREAN section and forceps delivery in same patient, 550
by incision of fundus, 1109
cases of, for eclampsia, 926
three successful, 733
Caffeine, action of, on mammalian heart, 541
Calomel in gonorrhœal arthritis, 356
Canaries, ringworm from, 183
Cancer Commission of Howard University, report of, 1110
lymphatic glands in, 730
of bile-ducts, 343
of Fallopian tubes, 548
of ovary, surgical treatment of, 359
of uterus, 180
hysterectomy for, 922
radical operations for, 1105
of viscera, 729
Cancerous infiltration of fibromyoma, 180
Carbolic acid in treatment of corneal ulcers, 1074
Carbon dioxide inhalation, influence of, upon body temperature, 917
Carcinoma of lips, 1095
of stomach, 341
Cardiac dilatation, 1101
primary, of Fallopian tube, 181
Carrefour sensitif, 444
Cartilaginous septum of nose, loss of, during convalescence from influenza, 746
Castration, end results of, for tuberculosis of testicles, 713
uterine, 1104
Cataract, depression of lens in, 739
Cell inclusions in cancer and in non-cancerous tissue, 1112
masses occurring in the so-called nævi of skin, source and significance of, 373
studies of Arnold, 748
Cellulitis of penis and scrotum, 16
Cerebro-spinal fluid in epileptics, 708
Chaulmoogra oil in lepra, 934
Chloroform narcosis, 549
Choked disk, pathogenesis of, 370
Cholecystitis and cholangitis of auto-infectious origin, 1091
acute, with gangrene, 193
Chorio-epithelioma of uterus, 549
Christian, H. M., chronic urethral discharge, 481
Circumcision as a preventive of syphilis and other disorders, 350
contraindication of, 1098

Cirrhosis of liver, operative treatment of, 169
Clark, F. S., meningitic cases in which Kernig's sign was absent, 783
Claytor, T. A., uncinariosis (ankylostomiasis), 28
Clitoris, spasms of, in tabes, 730
Coccidium infection of rabbit's liver, 1110
Coe, H. C., cases illustrating ureteral surgery, 1
Coleman, W., paratyphoid infections, 976
Concentrated light, action of, on the skin as a therapeutic agent, 934
Conservative vaginal compared with abdominal section, 362
Convergent squint, etiology and treatment of, 932
Corneal ulcers, recent methods of treating, 1074
Cretins and idiots, stigma of degeneration observed in, 1097
Crile, G. W., effect of severing and mechanically irritating the vagi, 652
Criminal abortion, attempted, in ectopic gestation, 1107
Croftan, A. C., experimental investigation into the causes and treatment of diabetes mellitus, 662
some experiments on the intermediary circulation of the bile acids, a contribution to our knowledge of icterus, 150
Cultural experiments of malignant tumors, 1111
Cumston, C. G., dermoid cyst of mouth, 491
Curettement and drainage of uterus for salpingitis, 359
Curtin, R. G., herpes zoster and its relation to internal inflammations and diseases, especially of the serous membranes, 264
Cyanide poisoning, antidotes for, 178
Cystinuria, transitory, associated with diaminuria, 838
Cysto-diagnosis and tuberculous meningitis, 344

DEAVER, J. B., causes of salpingitis other than gonorrhœal, 426
Decidua, formation of, in the Fallopian tube in tubal and intra-uterine pregnancy, 926
Deciduoma malignum, 552
Degeneration of the islands of Langerhans of the pancreas in diabetes mellitus, 706
Dementia præcox, case of, 109
Demodex folliculorum, 557
Dench, E. B., treatment of thrombosis of lateral sinus, following middle ear disease, 785
Dercum, F. X., hemianæsthesia of over eight years' duration, 444
Dermoid cyst of mouth, 491
Diabetes, 532
acid intoxication of, 533
and pregnancy, 1089
mellitus, 706
causes and treatment of, 662
phloridzin in, 916
Diet, proper, in treatment of chronic heart affections, 457
Digitalis and its allies, action of, upon the vessels, 916
Dimethyl sulphate, toxicity of, 918
Diphtheria antitoxin eruptions, 727
bacilli in noma, 172
use of artificial serum in, 720
Diplobacillus of Morax and Axenfeld, 284
Disseminated gangrene of skin in children, 183
Donohue, F. D., acute cholecystitis with gangrene, 193
Double hydrocele in an infant, 10
Duchenne's paralysis, case of, 552
Duke's, fourth disease of, confirmatory evidence in favor of, 172
Dunton, W. R., Jr., case of dementia præcox, 109
Duodenal ulcer in an infant, 719
Dysentery, acute, etiology of, 907
rare complications of, 536
Dysmenorrhœa, 728, 1104

ECHINOCOCCUS disease in North America, 124
Ectopic gestation, errors in diagnosis in, 182
treatment of, 363
with septic infection of the sac, 365
Eczema produced by formalin, 560
Ehrlich, lateral chain theory of, 881
Embolus following labor, 927
Emphysema, subcutaneous general, 719
Empyema of frontal sinus, 398
scarlatinous, 394
Endocarditis, acute, means of arresting, 356
Entero-anastomosis, 714
Enterocele, vaginal, 549
Epilepsy and its treatment, 725
Epileptics, cerebro-spinal fluid in, 708

Epityphlitis, operation for, in the free interval, 714
Eruptions due to orthoform, 934
Erythema nodosum, contagiousness of, 559
scarlatiniforme and true scarlatina in the course of diphtheria, 1099
Eshner, A. A., case of aortic insufficiency, with pericarditis, pleurisy, and mediastinitis, 1022
Ethyl and ethylene bromide, effects and after-effects of, 918
Exencephalic monster with bilateral harelip and cleft palate, 1061
Expectoration, albuminous, following thoracocentesis, 620
Experimental investigation into the causes and treatment of diabetes mellitus, 662
study of the effects of change of color upon pigment bacteria, 647

FACIAL paralysis after spontaneous labor, 366
Fallopian tube, carcinoma of, 181
tubes, cancer of, 548
Family periodic paralysis, case of, 163
Fever, malarial, 221
typhoid, 990
Fibrinous bronchitis, case of, 304
Fibroid tumors complicating pregnancy and labor, 366
of uterus, 731
uterus, retroversion of, 737
Fibroma molluscum, case of, 261
of abdominal wall, 361
Fibromyoma in cul-de-sac of Douglas, 728
Fibromyomata, treatment of, 920
Fibrous adhesions of the pericardium, pathology of, 241
Fibula, forward dislocation of head of, 285
Fischer, L., stomatitis gangrenosa, 643
Fistula, vesicovaginal, operation for, 547
Floods, sanitary measures to be adopted after, 485
Fluorescence of quinine and other remedies in the cure of malarial fever, 1025
Fœtus, prolonged retention of, 734
Formaldehyde, influence of, upon metabolism of children, 186
in milk, new test for, 562
Formic aldehyde, influence of, upon the metabolism of children, 166
Forward dislocation of head of fibula, 285
Fracture of a Gottstein curette during an operation for adenoids, 746
of patella, suture in, 715
Fractures of radius and ulna of both forearms, 616
Frank, L., primary tuberculosis of liver, 630
Frontal sinuitis, diagnosis of, 416
sinus, empyema of, 398
Fusiform bacillus of Vincent, 187

GAERTNER, F. W., an experimental investigation of puerperal pyæmia, 429
Gall-bladder, bacteriology of, 372
Gangrene after scarlatina, 719
of extremities after scarlet fever and other infectious diseases, 709
of extremity of left leg during convalescence from pneumonia, 538
of lungs, 375
Gastric ulcer and carcinoma, diagnostic value of blood examinations in, 342
treatment of, 543
Gastro-enteric disturbances, frequency of heredity in, 996
Gay, F. P., lateral chain theory of Ehrlich as explanatory of toxins, antitoxins, bacteriolysins, and hæmolysins, 881
Genital atresia, 919
Given, E. E. W., exencephalic monster with bilateral harelip and cleft palate, 1061
Glandular reaction in the diseases of children, 1097
Glaucoma, diagnosis and treatment of, 928
Glioma of retina, 370
Gonorrhœa and marriage, 730
Gonorrhœal arthritis, calomel in, 356
Goosegrease as an excipient in ringworm of scalp, 559
Gossage, A. M., etiology of infantile paralysis, 798
Gottstein curette, fracture of, during an operation for adenoids, 746
Gout, treatment of, 1102
Granular degeneration of the erythrocyte, 873
Granuloma, traumatic, of bladder, 1106
Green, F. R., phrenic nerve injuries, 196
Guaiacum, active principle of, 917

HÆMATOCELE due to hemorrhage from ovary, 921
retro-uterine, 181

Hand, A., Jr., typhoid fever treated in Children's Hospital of Philadelphia during 1901, 900
Hands, multiple ulcers of, due to occupation, 184
Harelip, 924
Hartzell, M. B., case of fibroma molluscum, 261
Hay fever and aristol, 724
Heart affections, chronic, dietary regimen in treatment of, 457
dilatation of, in children, 1102
disease and its treatment, 357
Hemianæsthesia, 444
Hemihypertonia postapoplectica, 794
Hemorrhage, retroplacental, 736
Hepatic lesions in infancy, 817
Heredity, frequency of, in gastro-enteric disturbances, 996
Herpes zoster, 264
origin and nature of, 141
Hot air in treatment of pelvic exudates, 922
Hydroa during pregnancy caused by staphylococcus albus, 923
Hydrocele, double, in an infant, 10
Hydrocephalus, chronic, treatment of, 355
Hydrophobia and the Pasteur methods, 354
Hydrosalpinx, etiology of, 182
Hypernephroma of kidney complicating pregnancy, 1069
Hyperplasia of the pharyngeal lymphoid tissue, 1031
Hysterectomy for cancer of the uterus, 922

ICTERUS, contribution to our knowledge of, 150
Idiopathic dilatation of œsophagus, 711
swelling of parotid gland in newborn infants, 550
Igasol, mechanism of action of, 542
Illoway, H., importance of proper dietary regimen in treatment of chronic heart affections, 457
Impacted calculus in the urethra in children, 16
Incipient carcinoma of the portio vaginalis, 361
Infancy, hepatic lesions in, 817
Infantile paralysis, etiology of, 798
pneumonia, a new sign of, 718
Infections, paratyphoid, 976
Infective diseases, review of some recent literature on certain, 288
Influenzal nephritis, 715
Inguinal glands, enlargement of, in cancer of viscera, 729
Iniencephalic monster, 1061
Injuries to phrenic nerve, 196
Interstitial pancreatitis, chronic, 845
Intestinal obstruction, auto-intoxication from, 539
perforation by ascaris lumbricoides, 905
Intestines, diseases of, 171
Intrapleural pressure in pneumothorax, 167
Intratracheal colloid struma, 1051
Intra-uterine rickets, 351
Intubation, 911
Intussusception in children, treatment of, 174
Iodic purpura, 726
Iodine and potassium iodide in malarial fever, 177
Iodopyrine, therapeutic indications of, 357
Iritis due to mumps, 742

JOPSON, J. H., impacted calculus in the urethra in children, 16
Jung, F. A. R., frequency of heredity in gastro-enteric disturbances, 996

KAKELS, M. S., primary sarcoma of tail of pancreas, 471
Kelly, A. O. J., review of some recent literature on certain infective diseases, 288
Keratitis due to mumps, 742
Kernig's sign as a symptom of focal brain disease, 772
absence of, in meningitic cases, 783
examination for, 781
Kidney, hypernephroma of, 1069
movable, etiology of, 732
Kidneys with reference to the employment of diuretics, 544
King, A. F. A., a new factor in the etiology of malarial fever, 221
fluorescence of quinine and other remedies in the cure of malarial fever, 1025
Kirkbride, M. B., new cabinet for microscopic slides, 869
Knock-knee, case of, 15

LABOR brought on by alcoholic neuritis, 735
Laparotomy for perforation in typhoid fever, 38

Lartigau, A. J., hyperplasia of the pharyngeal lymphoid tissue, 1031
Laryngitis, tuberculous, 747
Lateral chain theory of Ehrlich as explanatory of toxins, antitoxins, bacteriolysins, and hæmolysins, 881
Lead, effects of, upon lead-workers, 724
Le Conte, R. G., medical and surgical aspects of gangrene of the lung, 375
Lens, depression of, in cataract, 739
Lepra, injections of chaulmoogra oil in, 934
Lewis, M. W., transitory cystinuria associated with diaminuria, 838
Ligation of ureters, 921
Lipoma of pharynx, 746
Lips, carcinoma of, 1095
Liver, cirrhosis of, 169
  primary tuberculosis of, 630
Localization of the mental faculties in the left prefrontal lobe, 563, 751
Lung, gangrene of, 375
Lupus, 936
  carcinoma, 558
  erythematosus, etiology of, 557
    histopathology of, 935
Lymphatic glands in cancer, 730
  leukæmia, chronic, in an infant, 20
Lyon, I. P., a review of echinococcus disease in North America, 124

McCARTHY, D. J., hemihypertonia post-apoplectica, 794
McClintock, R. W., brain abscess in typhoid fever due to bacillus typhosus, 595
McFarland, J., hypernephroma of kidney complicating pregnancy, 1069
MacCoy, A. W., note on osteophytes of the nasal chambers, 286
Malaria, prophylaxis in, 177
  quinine in, 176
Malarial fever, 221, 1025
    treatment of, 177
  parasites and methylene blue, 179
Malignant tumors, 268
Mammalian heart, action of caffeine on, 541
Markoe, F. H., sacrococcygeal dimples, sinuses, and cysts, 820
Massage in sciatica, 355
Mastoid trephining operations, 603
Mayer, E., affections of the mouth and throat associated with the fusiform bacillus and spirillum of Vincent, 187
Measles, necrosis of lower jaw following, 14
Mechanism of the action of igasol, 542
Mediastinitis, 1022
Medication by latent arsenic, 175
Melæna neonatorum, gelatin injections in, 906
Meningitic cases, absence of Kernig's sign in, 783
Mental faculties, localization of, in the left prefrontal lobe, 563, 751
Mesenteric arteries, aneurism of, 1093
Metastatic ophthalmia in pneumonia, 742
Micro-organisms of the healthy and diseased conjunctiva, 369
  presence of, in the circulation during pneumonia, 346
Microscopic slides, new cabinet for, 869
Migrated ovarian and parovarian tumors, 731
Milk, bacterial contamination of, 937
  coagulation and digestion, observations upon, 352
  new test for formaldehyde in, 562
Mixed infection of typhoid fever and malaria, 532
Molluscum contagiosum, 1111
Monolateral innervation of the occipito-frontalis in a case of complete bilateral paralysis of the oculomotor nerves, 554
Monster, exencephalic, with bilateral hare-lip and cleft palate, 1061
Moore, E. K., causes of salpingitis other than gonorrhœal, 426
Morax and Axenfeld, diplobacillus of, 284
Morbid growths of nose, 746
    of upper air-passages, 747
Mouth and throat, affections of, 187
  dermoid cyst of, 491
Multiple neuritis, alcoholic, 811
  nodular melanocarcinoma of skin from a nævus, 933
  ulcers of hands due to occupation, 184
Mumps, iritis due to, 742
  keratitis due to, 742
  ocular, 742
    complications of, 369
  optic atrophy due to, 742
Mycosis of base of tongue, 745
  of palate, 745
  of tonsils, 745

NASAL chambers, osteophytes of, 286
Necrosis of lower jaw following measles, 14
Neuritis, alcoholic, 735

Neuritis treated by currents of high frequency, 355
Neuritis, optic, 1077
Neuroglia tissue, structure and histogenesis of, 749
Nicholson, W. R., present methods of treating ureters severed during abdominal operations, 676
Nicoll, M., Jr., hyperplasia of the pharyngeal lymphoid tissue, 1031
Night-terrors, pathogeny of, 353
Nodules, vocal, 747
Noma, 643
  diphtheria bacilli in, 172
  typhoid fever complicated by, 59
Non-meningitic cases, examination of, for Kernig's sign, 781
Nose, morbid growths of, 746

OBSERVATIONS on the nature of the Bence Jones albumin, 939
Ocular complications of mumps, 369
  of smallpox, 741
  mumps, 742
Œsophagus, idiopathic dilatation of, 711
Oleander, poisoning by, 725
Oliver, C. A., clinical history of a case of blindness from congenital deformity of the occiput, 4
  experimental study of the effects of change of color upon pigment bacteria, 647
Omentofixation, 537
Ophthalmia neonatorum, case of, 284
  complications of plague, 933
Ophthalmoscope, evolution of, 367
Opie, E. L., causes and varieties of chronic interstitial pancreatitis, 845
Optic atrophy due to mumps, 742
  neuritis, 1077
  thalmus, 444
Organo-therapy in treatment of fatty stools of pancreatic disease, 904
Osteomyelitis of tibia, acute, 13
Osteophytes of the nasal chambers, 286
Ovarian and parovarian tumors, 731
Ovary, cancer of, 359
Oxalates in urine, origin and prevention of deposits of, 705
Ozone, influence of, on bacteria, 185

PACKARD, F. A., medical and surgical aspects of gangrene of the lung, 375
Pancreas, sarcoma of tail of, 471
Pancreatic disease, fatty stools of, 904
  necrosis following trauma, 533
Pancreatitis, 168
Papilloma, diffuse, in larynx and trachea of a child, 747
Parakeratosis variegata, 935
Paralysis, infantile, etiology of, 798
  of facial and paralysis of lateral associated movements of the eyeballs, 740
  of stomach and intestines, 362
  of tongue, 745
Parametritis posterior, 929, 1106
Parasites, malarial, 179
Paratyphoid infections, 976
Patella, fracture of, 715
Pathogenesis of rhachitis, 174
Pathogenic torulæ, 1111
Pedicle, torsion of, in hydrosalpinx, 737
Pelvic abscess, vaginal incision in, 548
  disease, appendicitis in connection with, 546
  exudates, hot air in treatment of, 922
  organs, alcohol in treatment of, 181
Penis and scrotum, cellulitis of, 16
Pepper, W., further studies of granular degeneration of the erythrocyte, 873
Perforation of stomach, after-care of cases of, 711
  of uterus, 549
Pericarditis, 1022
  suppurative, 717
  tuberculous, 1008
Pericardium, pathology of the fibrous adhesions of, 241
Periodic paralysis, case of, 163
Periscopic lenses, 553
Peritonitis, post-operative, 182
Petroleum, crude, of no value in baldness, 934
Pharyngeal lymphoid tissue, hyperplasia of, 1031
  tonsil, tuberculosis of, 1031
Pharynx, lipoma of, 746
Phelps, C., localization of the mental faculties in the left prefrontal lobe, 563, 751
Phloridzin in diabetes, 916
Phosphorus therapy, value of, in rhachitis, 356
Phrenic nerve injuries, 196
Pigmentation of abdomen, 919
  of skin caused by the demodex folliculorum, 557
Placenta prævia, treatment of, 1107
Plague, ophthalmic complications of, 933

Pleurisy, 1022
Pneumonia, 538, 710
infantile, 718
metastatic ophthalmia in, 742
veratrum viride in, 722
Pneumothorax, intrapleural pressure in, 167
Poisoning by oleander, 725
Postpartum metastatic panophthalmitis, 743
Pregnancy and the climacteric, influence of, on ultimate results of operations for cancer, 729
early, fatal case of, 1108
parturition in a case complicated by advanced tabes dorsalis, 923
pernicious nausea of, 736
Prepuce, tuberculosis of, 558
Pressure of a pregnant uterus, death from, upon a horseshoe kidney, 927
Primary syphilitic optic neuritis, 1077
Prolapse of urethra, 1106
Prolapsed uterus, fixation of, 920
Prolapsus of rectum, 11
uteri, operation for, 362
Prophylactic perineotomy during labor, 551
Prophylaxis in malaria, 177
Pseudocyesis, 366
Pseudoligamentary ovarian tumors, 181
Puerperal pyæmia, 429
tetanus, 734
Pulmonary abscess, 347
hemorrhages and gelatin injections, 722
tuberculosis, association of, with both primary and secondary endocarditis, 93
Pupil in general disease, 738
Purification of water by sodium bisulphate, 562
Purpura following gonorrhœal infection, 558
iodic, 726
Purulent inflammation of the palpebral portion of the lacrymal gland, 744

QUININE as a prophylactic in malaria, 176
as a styptic and antiseptic, 915
in malarial fever, 1025
rash, 725

RADIUS and ulnar, fractures of, 616
Radix linguæ, sarcoma of, 115
Randall, B. A, modern mastoid trephining operations, 603
Rash, quinine, 725
Rectum, prolapsus of, 11
Relation between accidents and diabetes, 532
Renal tension and its treatment, 723
Report of the men working under the Cancer Commission of Howard University for the year 1901–1902, 1110
Retina, glioma of, 370
Retinal veins, visible blood current in, 743
Retroflexion, adherent, treatment of, 548
Retroplacental hemorrhage following traumatism in abdominal region, 736
Retro-uterine hæmatocele, 181
Retroversion of a fibroid uterus simulating pregnancy, 737
without symptoms, 360
Robinson, B., tuberculous pericarditis, 1008
Reviews—
Abbott, The Hygiene of Transmissible Diseases, 521
Abel, Gynecological Pathology, 897
Allchin, Manual of Medicine, 334
Bergey, Principles of Hygiene, 895
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Hare, Landis, Progressive Medicine, Vol. IV., 1901, 519
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Wolf, Laboratory Hand-book of Urine Analysis and Physiological Chemistry, 331
Rhachitis, pathogenesis of, 174
value of phosphorus therapy in, 356
Rheumatism, acute articular, 716
treatment of, 723
and allied disorders, 544
Rhinoscleroma, 746
Richards, G. L., empyema of the frontal sinus, 398
Rickets, intra-uterine, 351
Riesman, D., albuminous expectoration following thoracocentesis, 620
Rinehart, J. F., forward dislocation of head of fibula, 285
Ringworm from canaries, 183
of scalp, goosegrease in, 559
Robertson, W. E., thyroiditis complicating typhoid fever, 67
Robinson, B., angina pectoris, 225
Rosenmuller's gland, 744
Rosenow, E. C., association of stone and tumor of the urinary bladder, 634
Rupture of bladder, 539
of uterus, 925

SACROCOCCYGEAL dimples, sinuses, and cysts, 820
Sailer, J., two cases of typhoid fever complicated by noma, 59

Sailer J., unilateral occurrence of Kernig's sign as a symptom of focal brain disease, 772
Salpingitis, causes of, 426
chronic, indications for operation in, 729
drainage for, 359
Salpingotomy, 182
Sanitary measures to be adopted after floods, 485
Sarcoma of radix linguæ, 115
of tail of pancreas, 471
Scarlatina, gangrene after, 719
Scarlatinous empyema of the anterior superior squamomastoid cells, 394
Scarlet fever, gangrene of the extremities after, 709
Schley, W. S., sacrococcygeal dimples, sinuses, and cysts, 820
Schneiderlin's anæsthesia, 357
Schroeder, W. E., phrenic nerve injuries, 196
Sciatica, massage in, 355
surgical treatment of, 911
Sclerema neonatorum, etiology of, 559
Scott, J. A., case of chronic lymphatic leukæmia in an infant, 20
Serous meningitis due to typhoid bacillus, 718
Severing and mechanically irritating the vagi, effect of, 652
Shambaugh, G. E., diagnosis of latent frontal sinusitis, 416
sarcoma of radix linguæ, 115
Shields, W. G., Jr., examination for Kernig's sign, 781
Short-circuiting, merits of, in certain diseases of intestines, 171
Sidonal as an aid to uric-acid excretion, 356
Simon, C. E., observations on the nature of the Bence Jones albumin, 939
transitory cystinuria associated with diaminuria, 838
Skin, action of concentrated light on, 934
angioneuroses of, 935
disseminated gangrene of, 183
pigmentation of, caused by the demodex folliculorum, 557
Smallpox, ocular complications of, 741
Sodium silicate, sodium fluorsilicate, and sodium fluoride in therapeutics, 545
Soper, G. A., sanitary measures to be adopted after floods, 485
Spasm of clitoris in tabes, 730
Spiller, W. G., hemianæsthesia of over eight years' duration, 444
Spinal anæsthesia, 715
Spleen, surgery of, 349
Spondylitis, tubercular, 1095
Squint, convergent, 932
Stengel, A, further studies of granular degeneration of the erythrocyte, 873
Stenosis, tracheal, 1051
Sterilized cow's milk, increasing amount of fat in, 721
Stomach, after-care of cases of perforation of, 711
and intestines, paralysis of, 362
and liver, operations upon, 915
atrophy of, 1094
carcinoma of, 341
Stomatitis gangrenosa, 643
Stone and tumor, association of, of urinary bladder, 634
Strictures, tuberculous, of small intestine, 531
Strongyloides intestinalis in the United States, occurrence of, 707
Succinimide of mercury in treatment of syphilis, 546
Sulphate of copper in affections of the cornea and lids other than trachoma, 370
Suppurative pericarditis in children, 717
Supravascular pericardial nodules, 371
Surgery of spleen, 349
ureteral, cases illustrating, 1
Syphilis, blood and urine in, 1103
treatment of, by injections of succinimide of mercury, 546
Syphilitic enteritis under the form of melæna neonatorum, 1098
hydrarthrosis, 906
optic neuritis, 1077

TABES, spasms of clitoris in, 730
treatment of, 726
Test, new, for formaldehyde in milk, 562
Testicles, tuberculosis of, 713
Tetanus following vaginal fixation, 360
puerperal, 734
Tetramethylammonium chloride, action of, on circulation, 1101
Theisen, C. F., intratracheal colloid struma 1051
Theobald, S., observations upon recent methods of treating corneal ulcers, 1074
Therapeutic value of adrenalin chloride, 541

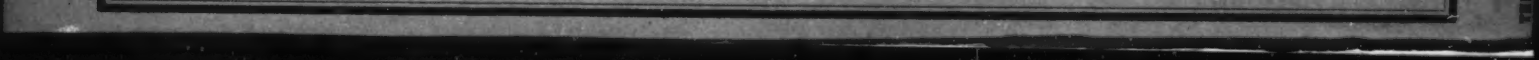
Thrombosis of lateral sinus, treatment of, 785
of varicose veins of leg, treatment of, 714
Thyroiditis complicating typhoid fever, 67
Tibia, acute osteomyelitis of, 13
Tongue, paralysis of, 745
Tonsil, pharyngeal, 1031
Torsion of pedicle in hydrosalpinx complicating pregnancy, 737
Toxicity of the cerebro spinal fluid in epileptics, 708
Tracheal stenosis, 1051
Traumatic intraperitoneal rupture of bladder, 539
Trephining operations, modern mastoid, 603
Trichinosis, frequency of in United States, 185
Tubercular spondylitis, 1095
Tuberculides, cutaneous, histopathology of two cases of, 560
Tuberculosis, blood in, 703
of pharyngeal tonsil, 1031
of prepuce, 558
of skin following accidental inoculation with bovine tubercle bacillus, 1092
of testicles, 713
primary, of liver, 630
uro-genital, 714
Tuberculous laryngitis, 747
meningitis, 344
pericarditis, 1008
peritonitis in children, 1094
strictures of small intestine, 531
Tumor of kidney, 1069
Tumors, malignant, 268
Typhoid bacillus, serous meningitis due to, 718
fever and malaria, mixed infection of, 532, 990
brain abscess in, due to bacillus typhosus, 595
complicated by noma, 59
in infancy and childhood, 352
laparotomy for perforation in, 38
myocarditis in children, treatment of, 1099

ULCER, duodenal, in an infant, 719
gastric, treatment of, 543
Ulcers corneal, recent methods of treating, 1074
of hands due to occupation, 184
Uncinariosis, 28
Uræmic ulceration of stomach and small intestine, 909
Ureteral surgery, cases illustrating, 1
Ureters, ligation of, 921
present methods of treating, severed during abdominal operations, 676
Urethra, female, new formation of, 732
in children, impacted calculus in, 16
prolapse of, 1106
Urethral discharge, chronic, 481
Urethritis, acute, due to the staphylococcus, 538
Uric-acid excretion, sidonal as an aid to, 356
Urinary bladder, association of stone and tumor of, 634
Urine, oxalates in, 705
Uro-genital tuberculosis, experimental, 714
Uterine cancer, extension of, through lymphatics, 182
diagnosis of, 921
statistics of, 728
castration, 1104
fibroids, origin of, 180
operations for, 921
Uterus, atony of, 737
cancer of, 180, 1105
chorio-epithelioma of, 549
fibroid tumors of, 731
perforation of, 549
rupture of, 925

VAGI, effect of severing and of mechanically irritating, 652
Vaginal enterocele, posterior, 549
hysterectomy as a radical operation for cancer of uterus, 361
incision in pelvic abscess, 548
puncture and incision, 1105
Valerian, some new preparations of, 723
Van Harlingen, A., recent views of the origin and nature of herpes zoster, 141
Varicose veins of leg, thrombosis of, 714
Veasey, C. A., primary syphilitic optic neuritis, 1077
Vegetations, adenoid, 720
Veratrum viride in pneumonia, 722
Vesical and ureteral fistulæ following vaginal hysterectomy, 922
Vesicovaginal fistula, operation for, 547
Vesiculæ seminales, excision of, for primary tuberculous disease, 910
Vincent, fusiform bacillus of, 187

Viscera, cancer of, 729
Visible blood current in retinal veins in leukæmia, 743
Vocal nodules, 747

WATER, purification of, 562
Wells, H. G., pathology of the healed fibrous adhesions of the pericardium, 241
Walker, John K., typhoid fever treated in Children's Hospital of Philadelphia during 1901, 990
Westphal-Piltz pupil phenomenon, 342
Wharton, H. R., clinical lecture, 10
White, C. Y., further studies of granular degeneration of the erythrocyte, 873
Wollstein, M., hepatic lesions in infancy, 817



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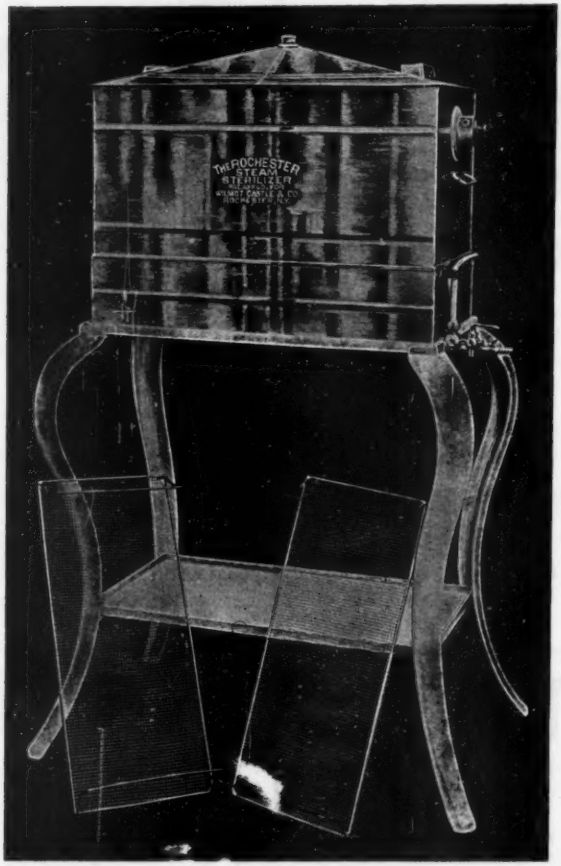

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CONTENTS.

ORIGINAL COMMUNICATIONS.

PAGE

Observations on the Nature of the Bence Jones Albumin. By CHARLES E. SIMON, M.D. 939

Paratyphoid Infections. By WARREN COLEMAN, M.D., and B. H. BUXTON, M.D. 976

An Analysis of Seventy-one Cases of Typhoid Fever Treated in the Children's Hospital of Philadelphia during 1901. By ALFRED HAND, JR., M.D., and JOHN K. WALKER, M.D. 990

The Frequency of Heredity in Gastro-enteric Disturbances. By FRANZ A. R. JUNG, M.D. 996

Tuberculous Pericarditis. By BEVERLEY ROBINSON, M.D. . . 1008

A Case of Aortic Insufficiency, with Pericarditis, Pleurisy, and Mediastinitis. By AUGUSTUS A. ESHNER, M.D. 1022

The Fluorescence of Quinine and Other Remedies in the Cure of Malarial Fever. By A. F. A. KING, M.D. 1025

A Study of Hyperplasia of the Pharyngeal Lymphoid Tissue (Adenoids), with Especial Reference to Primary Tuberculosis of the Pharyngeal Tonsil. By AUGUST JEROME LARTIGAU, M.D., and MATTHIAS NICOLL, JR., M.D. 1031

A Case of Intratracheal Colloid Struma; Operation; Recovery. By CLEMENT F. THEISEN, M.D. 1051

Exencephalic (Iniencephalic ?) Monster with Bilateral Harelip and Cleft Palate. By ELLIS E. W. GIVEN, M.D. 1061

A Case of Hypernephroma of the Kidney Complicating Pregnancy. By GEORGE M. BOYD, M.D., and JOSEPH MCFARLAND, M.D. . 1069

Observations upon Recent Methods of Treating Corneal Ulcers, with Especial Reference to the Use of Carbolic Acid as a Not Infrequent Substitute for the Actual Cautery. By SAMUEL THEOBALD, M.D. 1074

Primary Syphilitic Optic Neuritis. By C. A. VEASEY, A.M., M.D. . 1077

REVIEWS.

PAGE

The Practice of Obstetrics, by American Authors. By Charles Jewett, M.D. 1081

An American Text-book of Pathology. By Ludvig Hektoen, M.D., and David Riesman, M.D. 1084

Progressive Medicine. By Hobart Amory Hare, M.D. 1086

A Text-book of Diseases of Women. By Charles B. Penrose, M.D., Ph.D. 1087

Modern Obstetrics, General and Operative. By W. A. Newman Dorland, A.M., M.D. 1088

PROGRESS OF MEDICAL SCIENCE.

MEDICINE.

UNDER THE CHARGE OF

WILLIAM OSLER, M.D.,

AND

W. S. THAYER, M.D.

PAGE

Diabetes and Pregnancy . . 1089

Apparent Contagion in Rheumatism Due to Meyer's Diplococcus 1090

Cholecystitis and Cholangitis . 1091

PAGE

A Case of Tuberculosis of the Skin following Accidental Inoculation with the Bovine Tubercle Bacillus 1092

SURGERY.

UNDER THE CHARGE OF

J. WILLIAM WHITE, M.D.,

AND

F. D. PATTERSON, M.D.

Aneurism of the Mesenteric Arteries 1093

The Diagnosis of Tuberculous Peritonitis in Children . . 1094

Complete Atrophy of the Stomach 1094

Carcinoma of the Lips . . 1095

What is the Prognosis in Tubercular Spondylitis? . . . 1095

PEDIATRICS.

UNDER THE CHARGE OF

LOUIS STARR, M.D.,

AND

THOMPSON S. WESTCOTT, M.D.

	PAGE		PAGE
Glandular Reaction in the Diseases of Children	1097	Contraindication to Circumcision	1098
A Stigma of Degeneration Observed in Cretins and Idiots	1097	Treatment of Typhoid Myocarditis in Children	1099
Syphilitic Enteritis under the Form of Melæna Neonatorum	1098	Erythema Scarlatiniforme and True Scarlatina in the Course of Diphtheria	1099

THERAPEUTICS.

UNDER THE CHARGE OF

REYNOLD WEBB WILCOX, M.D., LL.D.,

AND

SMITH ELY JELLIFFE, M.D., PH.D.

Adrenal Extracts and Hæmatemesis	1100	Treatment of Cardiac Dilatation	1101
Action of Tetramethyl Ammonium Chloride on Circulation	1101	Dilatation of Heart in Children	1102
		The Treatment of Gout	1102
		Blood and Urine in Syphilis	1103

GYNECOLOGY.

UNDER THE CHARGE OF

HENRY C. COE, M.D.,

ASSISTED BY

WILLIAM E. STUDDIFORD, M.D.

Dysmenorrhœa	1104	Vaginal Puncture and Incision	1105
Apparent Abdominal Tumors	1104	Antero-lateral Colpotomy	1105
Uterine Castration	1104	Prolapse of the Urethra	1106
Operations for Cancer of Uterus	1105	Parametritis Posterior	1106
Treatment of Inoperable Cancer of the Uterus	1105	Traumatic Granuloma of the Bladder	1106

OBSTETRICS.

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.

	PAGE		PAGE
Attempted Criminal Abortion in Ectopic Gestation . . .	1107	Complicated and Fatal Pregnancy	1108
The Treatment of Placenta Prævia	1107	Cæsarean Section by Incision of the Fundus	1109

PATHOLOGY AND BACTERIOLOGY.

UNDER THE CHARGE OF

F. B. MALLORY, M.D.

Report of the Men Working under the Cancer Commission of Harvard University for the Year 1901–1902 1110

INDEX 1115

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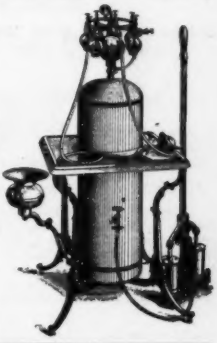

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